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Fig. 1 Cleavage and Polyadenylation Process For The
SV40 early Poly(A) site

A. CTTATCGATACCGTCGAAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCAT
CACAAATTTACAAATAAAGCATTCTAGTTGTGGTTTGTCCAAACTCATCA
+++++ ↑ +++++
ATGTATCTTATCATGTC (Seq ID NO:1) Cleavage site

B. AAUAAA
+++++ GCA

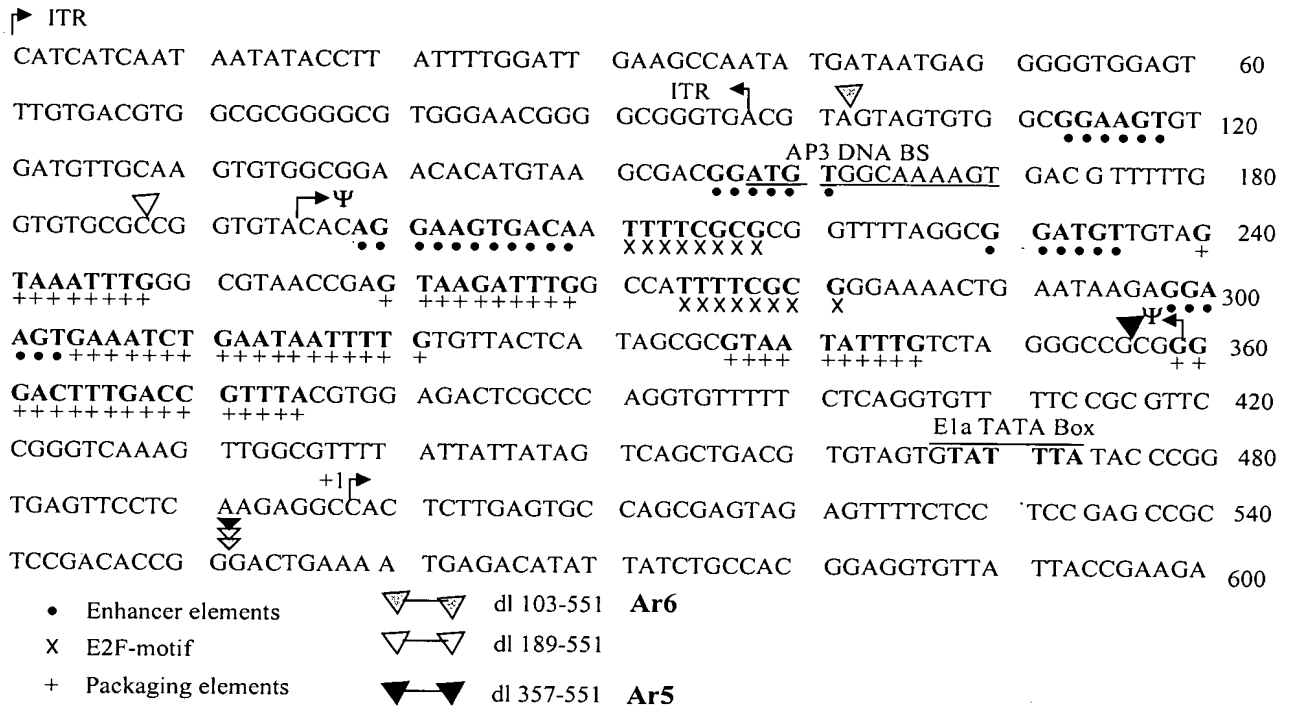
C. GCAaaaaaaaaaaaaaaaaaaaaa (Seq ID NO:18)

+ Upstream and downstream
cleavage-polyadenylation elements

10081969.022202

(Seq ID NO:2)

Fig 2 E1A transcription control region



10081969-022200

Figure 3. Sequence of Ar6pAE2fF from left and right ends of viral DNA

A. Nucleotides 1-1802 containing ITR, polyA, E2F-1 promoter, E1a and a portion of the E1b gene (Seq ID NO:3)

1 CATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAGGGGGTGGAGT
+-----ITR-----
61 TTGTGACGTGGCGCGGGCGTGGGAACGGGGCGGGTGACGTAGGGCGCGATCAAGCTTAT
+-----ITR-----+
121 CGATACCGTCGAAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCATC
-----polyA-----
181 ACAAATTTACAAATAAAGCATTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAAACTC
-----polyA-----
241 ATCAATGTATCTTATCATGTCTGGATCCGCGCCGCTAGCGATCATCCGGACAAAGCCTGC
-----+-----
301 GCGCGCCCCGCCCCGCCATTGGCCGTACCGCCCCGCGCCGCGCCCATCTCGCCCCCTCG
-----E2F-1 promoter-----
361 CCGCCGGGTCCGGCGCGTTAAAGCCAATAGGAACCGCCCGTGTTCCTCGTCACGGCCG
-----E2F-1 promoter-----
421 GGGCAGCCAATTGTGGCGGCGCTCGGCGGCTCGTGGCTCTTTCGCGGCAAAAAGGATTTG
-----E2f-1 promoter-----
481 GCGCGTAAAAGTGGCCGGGACTTTGCAGGCAGCGGCGCGGGGGCGGAGCGGGATCGAG
-----E2f-1 promoter-----
541 CCCTCGATGATATCAGATCATCGGATCCCGGTCTGACTGAAAATGAGACATATTATCTGCC
-----+-----
601 ACGGAGGTGTTATTACCGAAGAAATGGCCGCCAGTCTTTTGGACCAGCTGATCGAAGAGG
-----E1a gene-----
661 TACTGGCTGATAATCTTCCACCTCCTAGCCATTTTGAACCACCTACCCTTCACGAACTGT
-----E1a gene-----
721 ATGATTTAGACGTGACGGCCCCCGAAGATCCCAACGAGGAGGCGGTTTCGCAGATTTTTC
-----E1a gene-----
781 CCGACTCTGTAATGTTGGCGGTGCAGGAAGGGATTGACTTACTCACTTTTCCGCCGGCGC
-----E1a gene-----
841 CCGGTTCTCCGGAGCCGCTCACCTTTCCCGGCAGCCCGAGCAGCCGGAGCAGAGAGCCT
-----E1a gene-----
901 TGGGTCCGGTTTCTATGCCAAACCTTGTACCGGAGGTGATCGATCTTACCTGCCACGAGG
-----E1a gene-----

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961 CTGGCTTTCCACCCAGTGACGACGAGGATGAAGAGGGTGAGGAGTTTGTGTTAGATTATG
-----Ela gene-----
1021 TGGAGCACCCCGGGCACGGTTGCAGGTCCTGTTCATTATCACCGGAGGAATACGGGGGACC
-----Ela gene-----
1081 CAGATATTATGTGTTCGCTTTGCTATATGAGGACCTGTGGCATGTTTGTCTACAGTAAGT
-----Ela gene-----
1141 GAAAATTATGGGCAGTGGGTGATAGAGTGGTGGGTTTGGTGTGGTAATTTTTTTTTTTAAT
-----Ela gene-----
1201 TTTTACAGTTTTGTGGTTTAAAGAATTTTGTATTGTGATTTTTTTTAAAAGGTCCTGTGTC
-----Ela gene-----
1261 TGAACCTGAGCCTGAGCCCCGAGCCAGAACCGGAGCCTGCAAGACCTACCCGCCGTCCTAA
-----Ela gene-----
1321 AATGGCGCCTGCTATCCTGAGACGCCCCGACATCACCTGTGTCTAGAGAATGCAATAGTAG
-----Ela gene-----
1381 TACGGATAGCTGTGACTCCGGTCCTTCTAACACACCTCCTGAGATACACCCGGTGGTCCC
-----Ela gene-----
1441 GCTGTGCCCCATTAAACCAGTTGCCGTGAGAGTTGGTGGGCGTCGCCAGGCTGTGGAATG
-----Ela gene-----
1501 TATCGAGGACTTGCTTAACGAGCCTGGGCAACCTTTGGACTTGAGCTGTAAACGCCCCAG
-----Ela gene-----
1561 GCCATAAGGTGTAAACCTGTGATTGCGTGTGTGGTTAACGCCTTTGTTTGCTGAATGAGT
-----Ela gene-----
1621 TGATGTAAGTTTAAATAAAGGGTGAGATAATGTTTAACTTGCATGGCGTGTTAAATGGGGC
-----+-----
1681 GGGGCTTAAAGGGTATATAATGCGCCGTGGGCTAATCTTGGTTACATCTGACCTCATGGA
-----E1b gene-----
1741 GGCTTGGGAGTGTTTGGAAGATTTTTCTGCTGTGCGTAACTTGCTGGAACAGAGCTCTAA
-----E1b gene-----
1801 CA
--

B. Nucleotides 33881-34412 containing packaging signal and ITR (Seq ID NO:4)

33881 AACCTACGCCAGAAACGAAAGCCAAAAACCCACAACCTTCCTCAAATCGTCACTTCCGT
33941 TTTCCACGTTACGTCACTTCCCATTTTAATTAAGAATTCTACAATTCCCAACACATACA

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34001 AGTTACTCCGCCCTAAAACCTGGGCGAGTCTCCACGTAAACGGTCAAAGTCCCCGCGGC
+--packaging signal-----
34061 CCTAGACAAATATTACGCGCTATGAGTAACACAAAATTATTCAGATTTCACTTCCTCTTA
-----packaging signal-----
34121 TTCAGTTTTCCCGCGAAAATGGCCAAATCTTACTCGGTTACGCCCAAATTTACTACAACA
-----packaging signal-----
34181 TCCGCCTAAAACCGCGCGAAAATTGTCACCTTCCTGTGTACACCGGCGCACACCAAAAACG
-----+
34241 TCACTTTTGCCACATCCGTCGCTTACATGTGTTCCGCCACACTTGCAACATCACACTTCC
34301 GCCACACTACTACGTCACCCGCCCCGTTCCACGCCCGCGCCACGTCACAAACTCCACC
+----- ITR-----
34361 CCCTCATTATCATATTGGCTTCAATCCAAAATAAGGTATATTATTGATGATG
----- ITR-----+

1.0081969.022203

Figure 4. Sequence of Ar6F from left end of viral DNA (Seq ID NO:5)

1 CATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAGGGGGTGGAGT
+-----ITR-----

61 TTGTGACGTGGCGCGGGGCGTGGGAACGGGGCGGGTGACGTAGGGCGCGCCGCTAGCGAT
-----ITR-----++-----MCS-----

121 ATCGGATCCCGGTCGACTGAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGA
-----+-----E1a-----

181 AGAAATGGCCGCCAGTCTTTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCC
-----E1a-----

241 ACCTCCTAGCCATTTTGAACCACCTACCCTTCACGAACTGTATGATTTAGACGTGACGGC
-----E1a-----

301 CCCC GAAGATCCCAACGAGGAGGCGGTTTTCGCAGATTTTTC CCGACTCTGTAATGTTGGC
-----E1a-----

361 GGTGCAGGAAGGGATTGACTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCC
-----E1a-----

421 TCACCTTTCCCGGCAGCCCGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCC
-----E1a-----

481 AAACCTTGTACCGGAGGTGATCGATCTTACCTGCCACGAGGCTGGCTTTCCACCCAGTGA
-----E1a-----

541 CGACGAGGATGAAGAGGGTGAGGAGTTTGTGTTAGATTATGTGGAGCACCCCGGGCACGG
-----E1a-----

601 TTGCAGGTCTTGTCATTATCACCGGAGGAATACGGGGGACCCAGATATTATGTGTTTCGCT
-----E1a-----

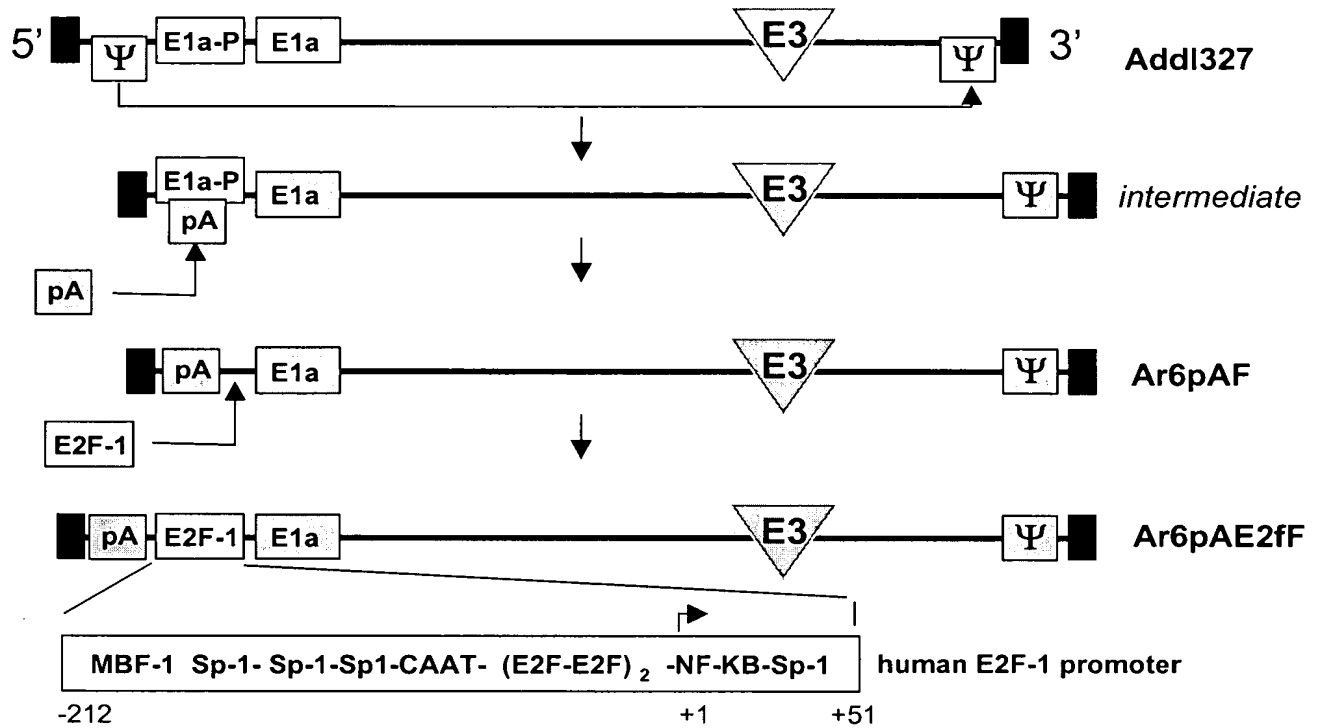
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Figure 5. Sequence of Ar6pAF from left end of viral DNA (Seq ID NO:6)

1 CATCATCAATAATATACCTTATTTTGGATTGAAGCCAATATGATAATGAGGGGGTGGAGT
+-----ITR-----
61 TTGTGACGTGGCGCGGGGCGTGGGAACGGGGCGGGTGACGTAGGGCGCGATCAAGCTTAT
-----ITR-----+ +---
121 CGATACCGTCGAAACTTGTTTATTGCAGCTTATAATGGTTACAAATAAAGCAATAGCATC
-----polyA-----
181 ACAAATTTACAAATAAAGCATTTTTTTTCACTGCATTCTAGTTGTGGTTTGTCCAACTC
-----polyA-----
241 ATCAATGTATCTTATCATGTCTGGATCCGCGCCGCTAGCGATATCGGATCCCGGTGCGACT
-----+ +---
301 GAAAATGAGACATATTATCTGCCACGGAGGTGTTATTACCGAAGAAATGGCCGCCAGTCT
-----E1a-----
361 TTTGGACCAGCTGATCGAAGAGGTACTGGCTGATAATCTTCCACCTCCTAGCCATTTTGA
-----E1a-----
421 ACCACCTACCCTTCACGAACTGTATGATTAGACGTGACGGCCCCCGAAGATCCCAACGA
-----E1a-----
481 GGAGGCGGTTTTCGCAGATTTTTCCCGACTCTGTAATGTTGGCGGTGCAGGAAGGGATTGA
-----E1a-----
541 CTTACTCACTTTTCCGCCGGCGCCCGGTTCTCCGGAGCCGCCTCACCTTTCCCGGCAGCC
-----E1a-----
601 CGAGCAGCCGGAGCAGAGAGCCTTGGGTCCGGTTTCTATGCCAAACCTTGTACCGGAGGT
-----E1a-----

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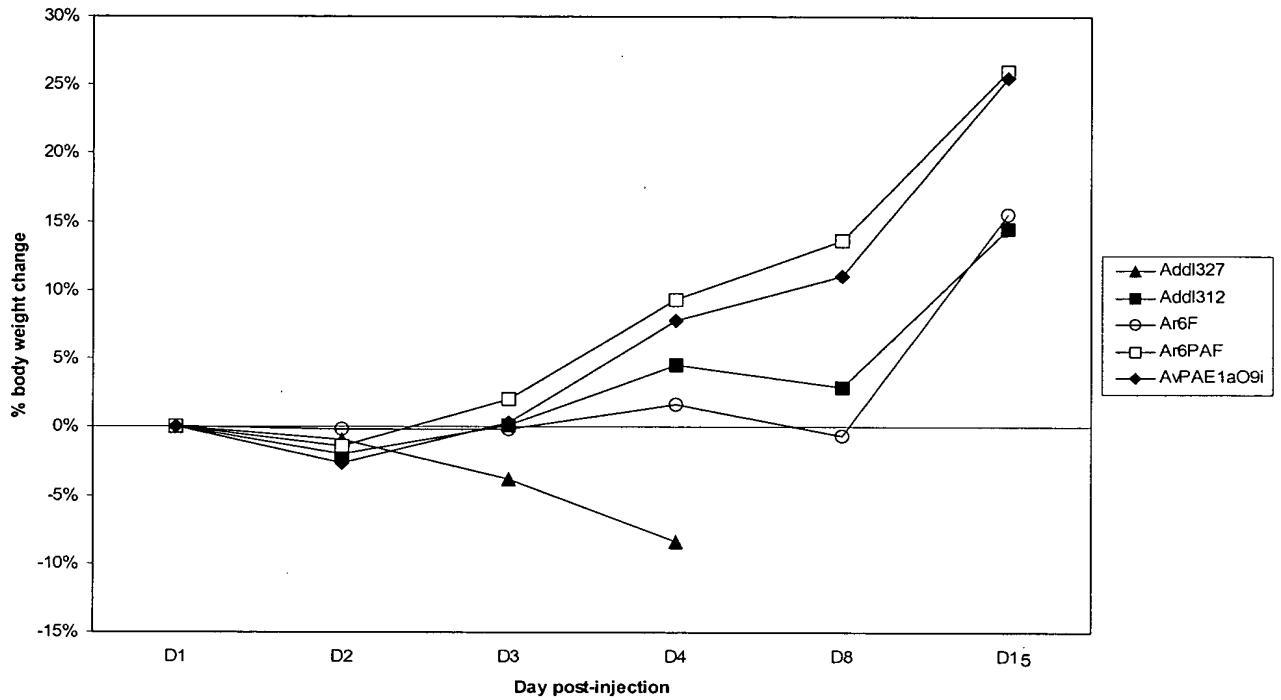
Figure 6. Schematic diagram of Ar6pAF and Ar6pAE2fF vectors



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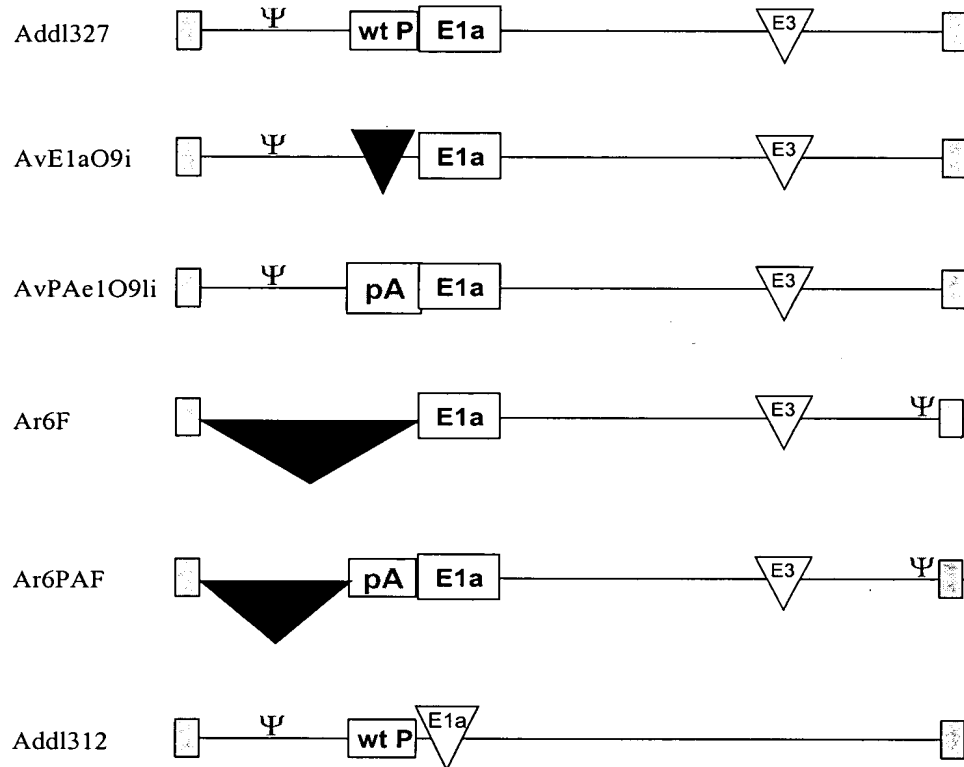
Fig. 7 Body weight change



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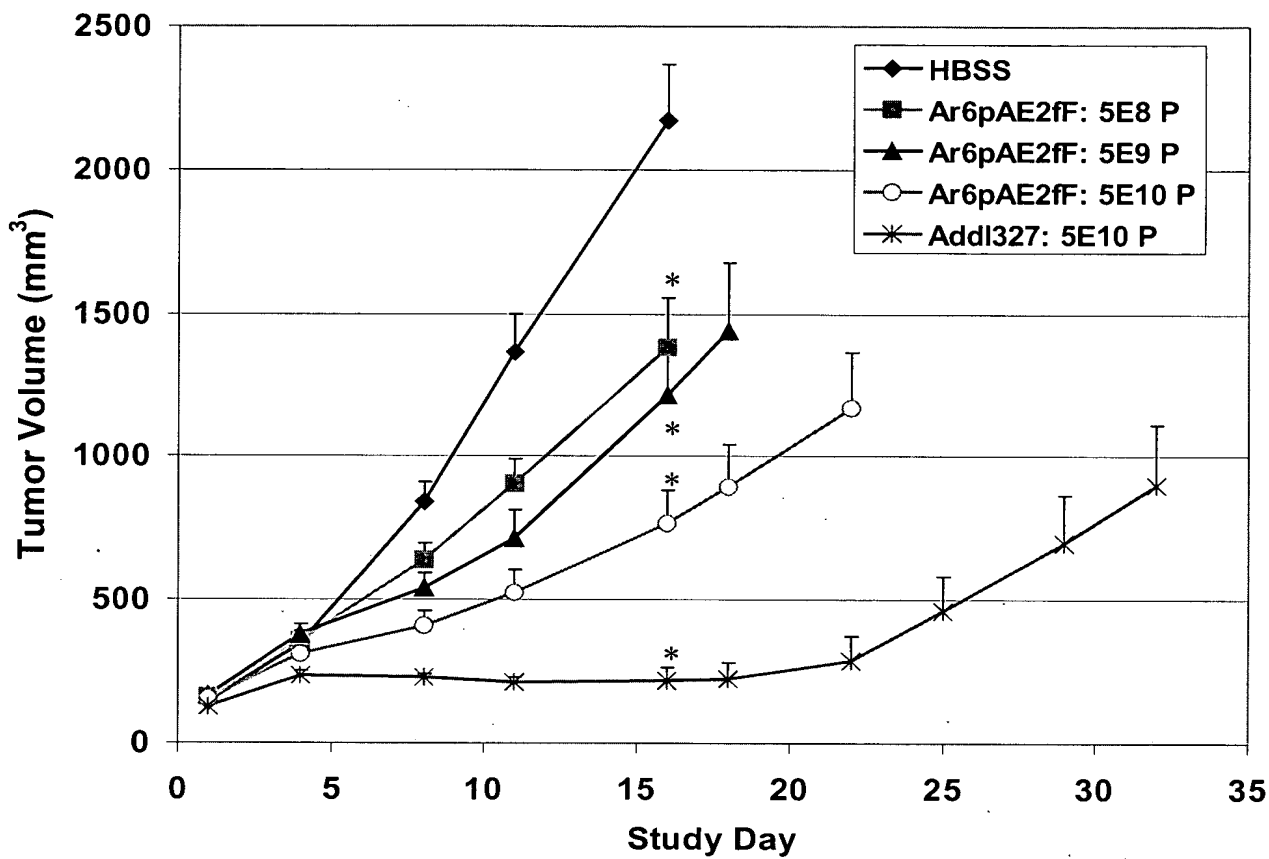
Fig. 8 Minimizing nonspecific transactivation of E1a gene

Backbones generated:



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Figure 9. Mean H460 tumor volume



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Figure 10. Survival following intratumoral administration of vectors to H460 tumors

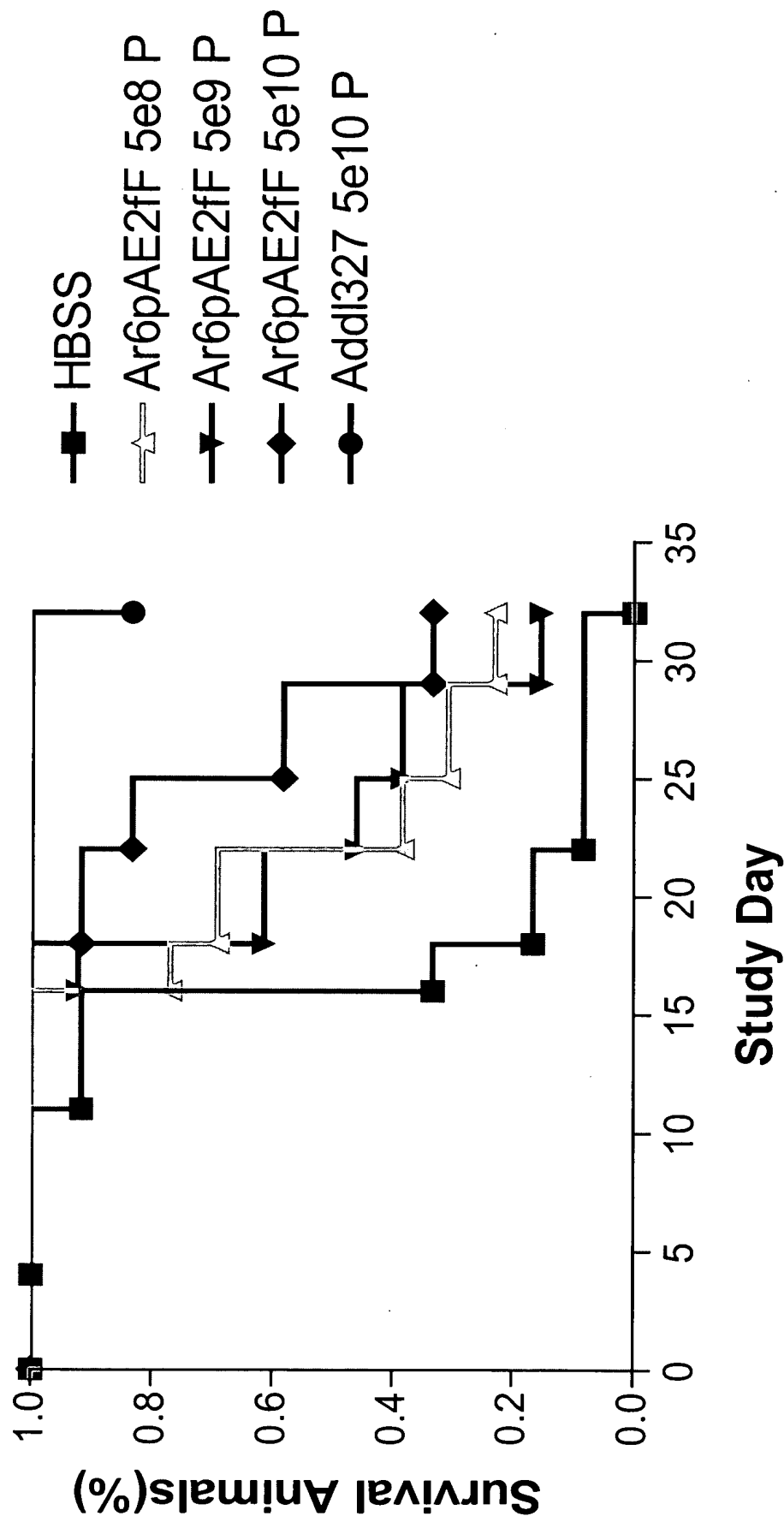
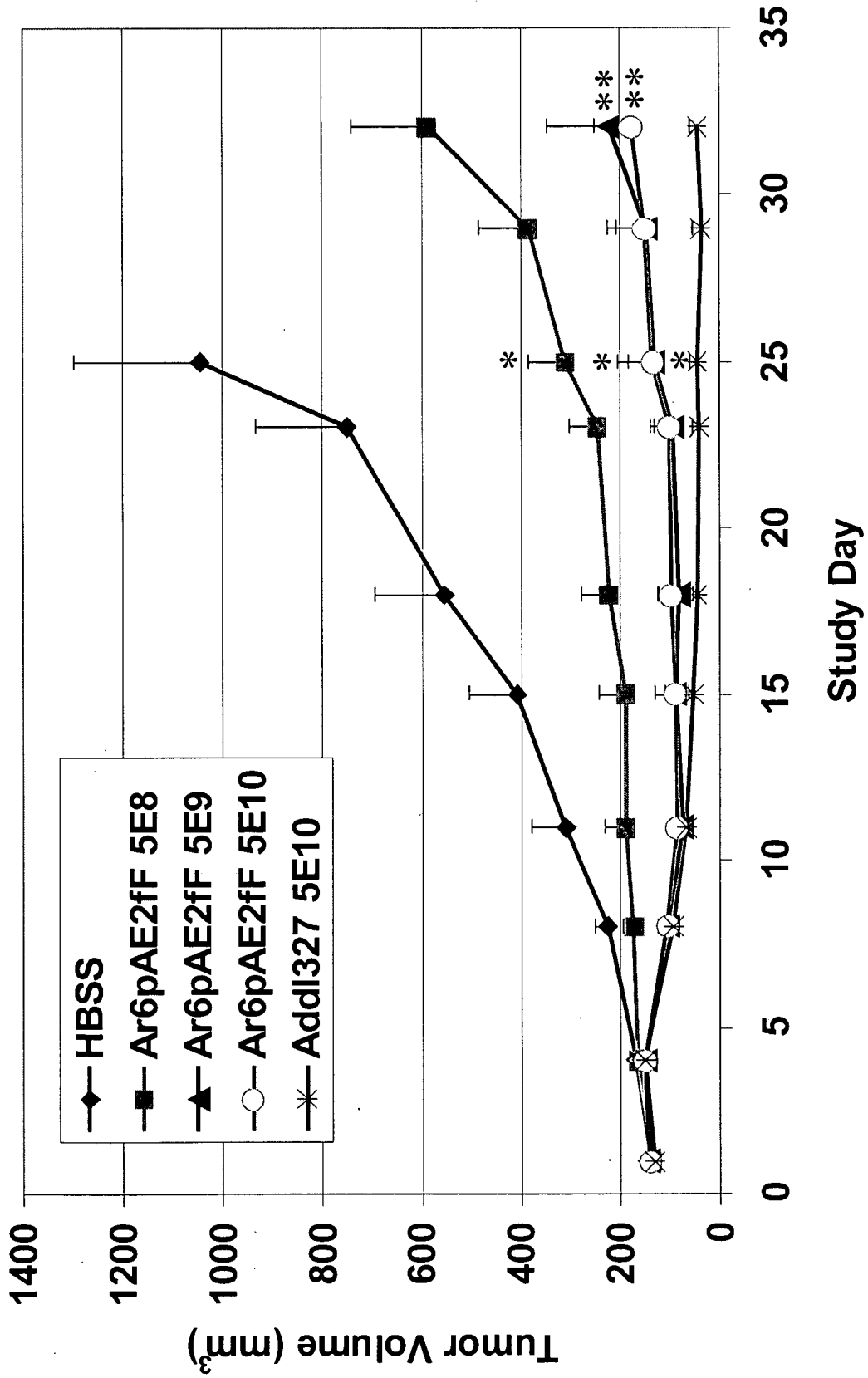
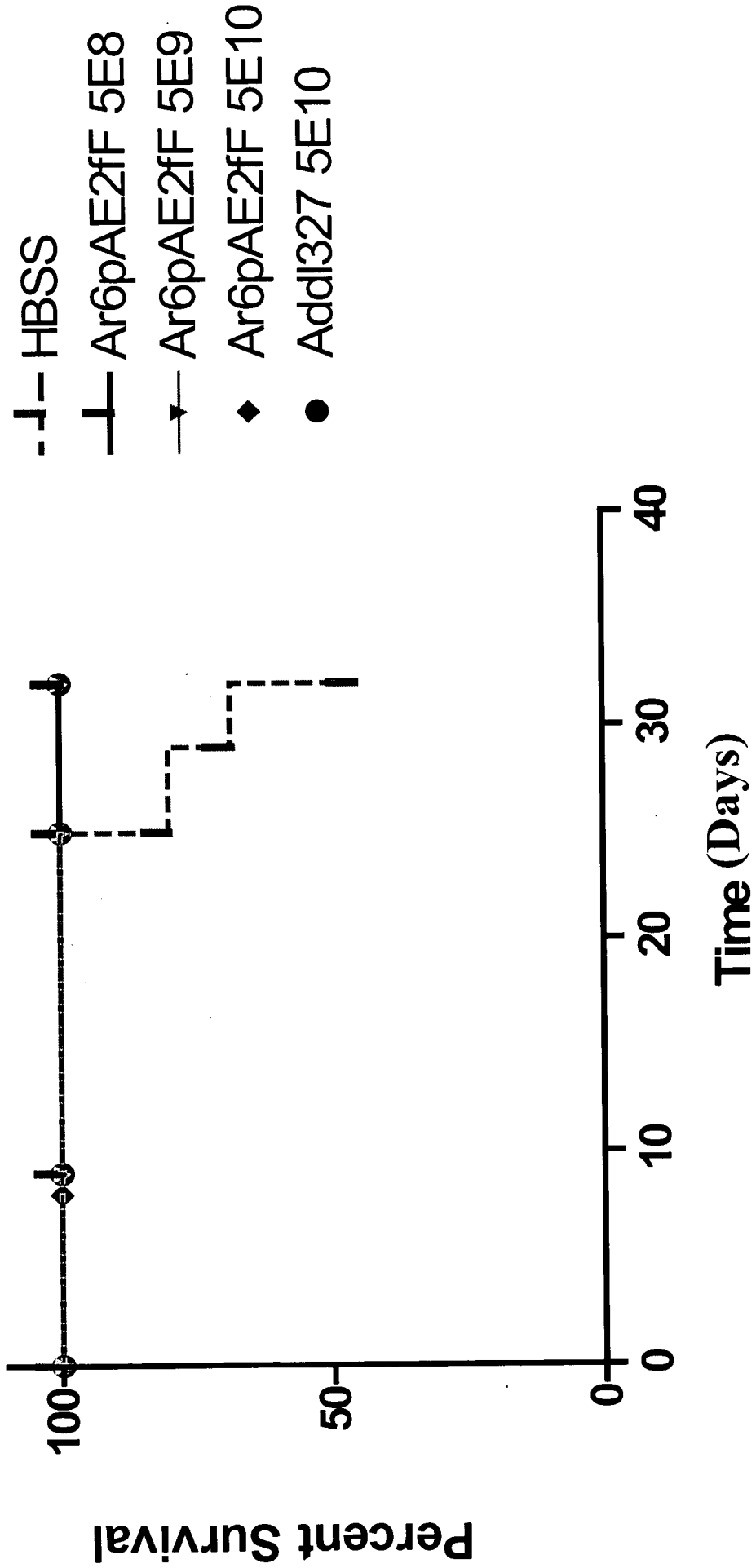


Figure 11. Mean Hep3B tumor volumes



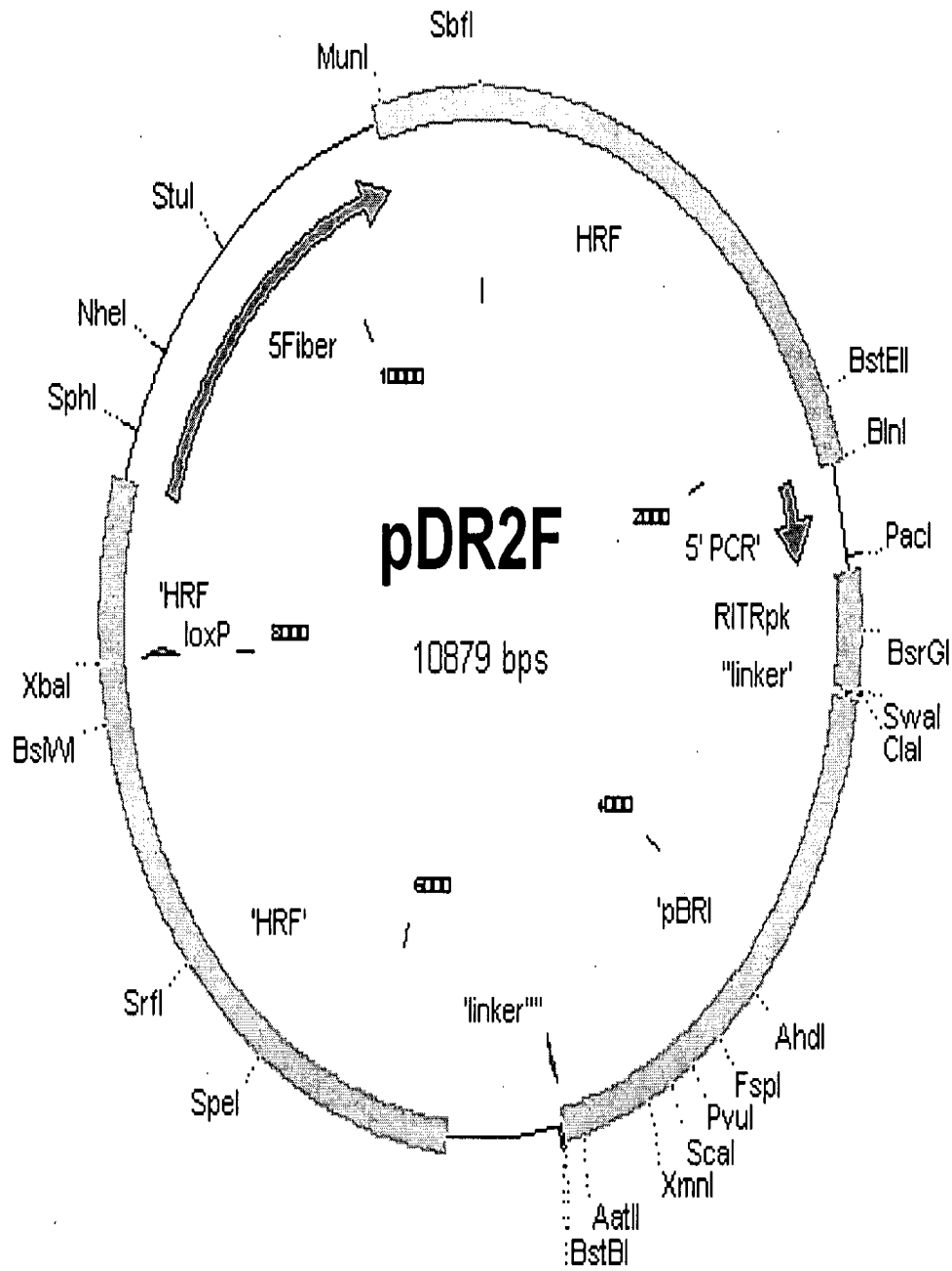
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Figure 12. Survival following intratumoral administration of vector to Hep3B tumors



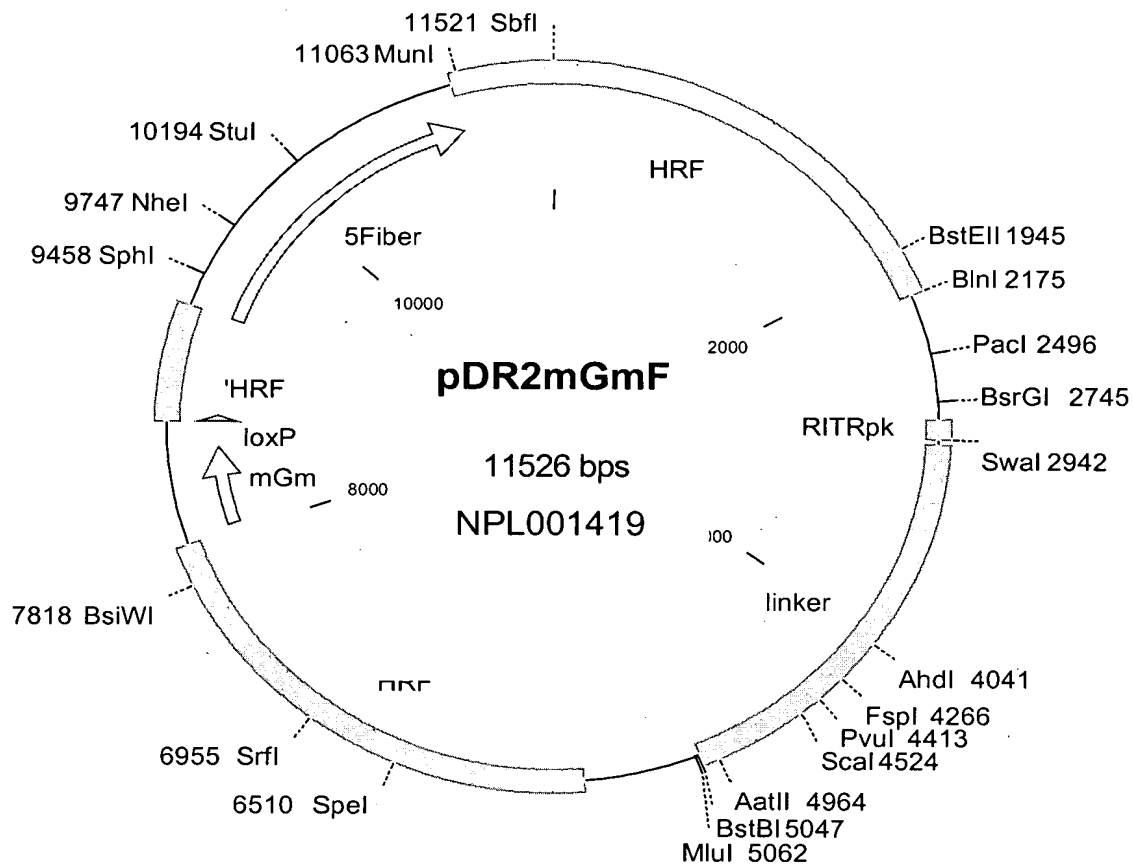
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Figure 13. Schematic diagram of adenovirus right donor plasmid pDR2F.



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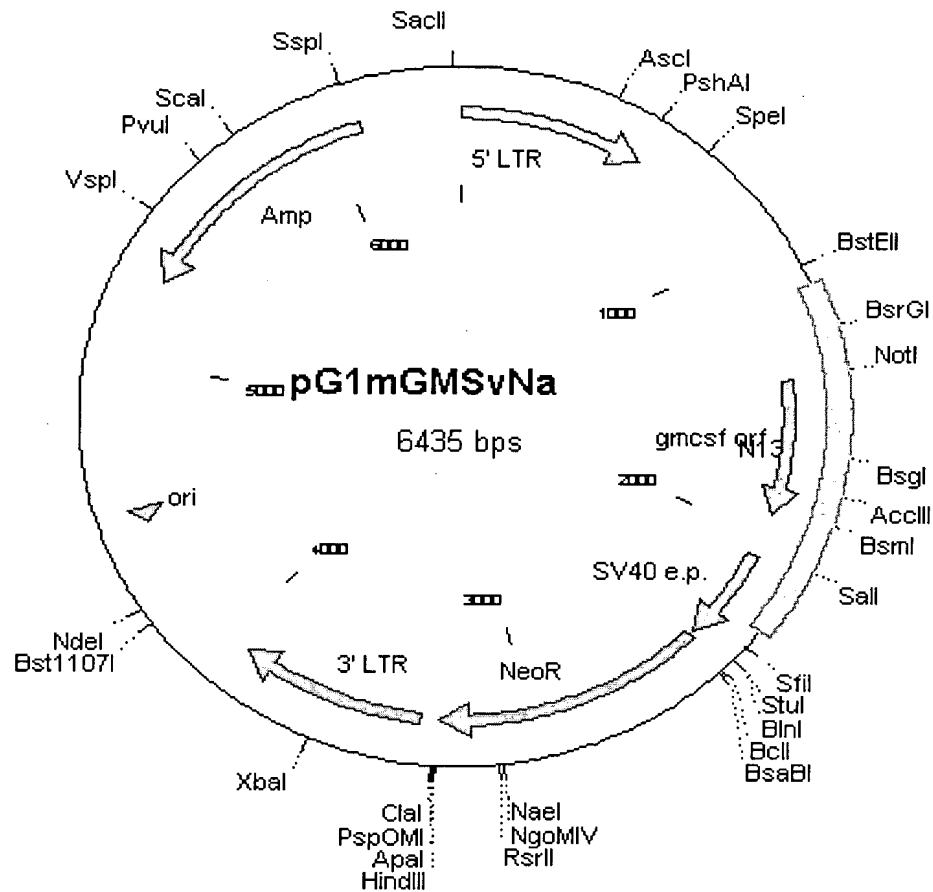
Figure 14. Schematic diagram of adenovirus right donor plasmid pDR2mGmF.



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Figure 15. Schematic diagram of plasmid pG1mGmSvNa.

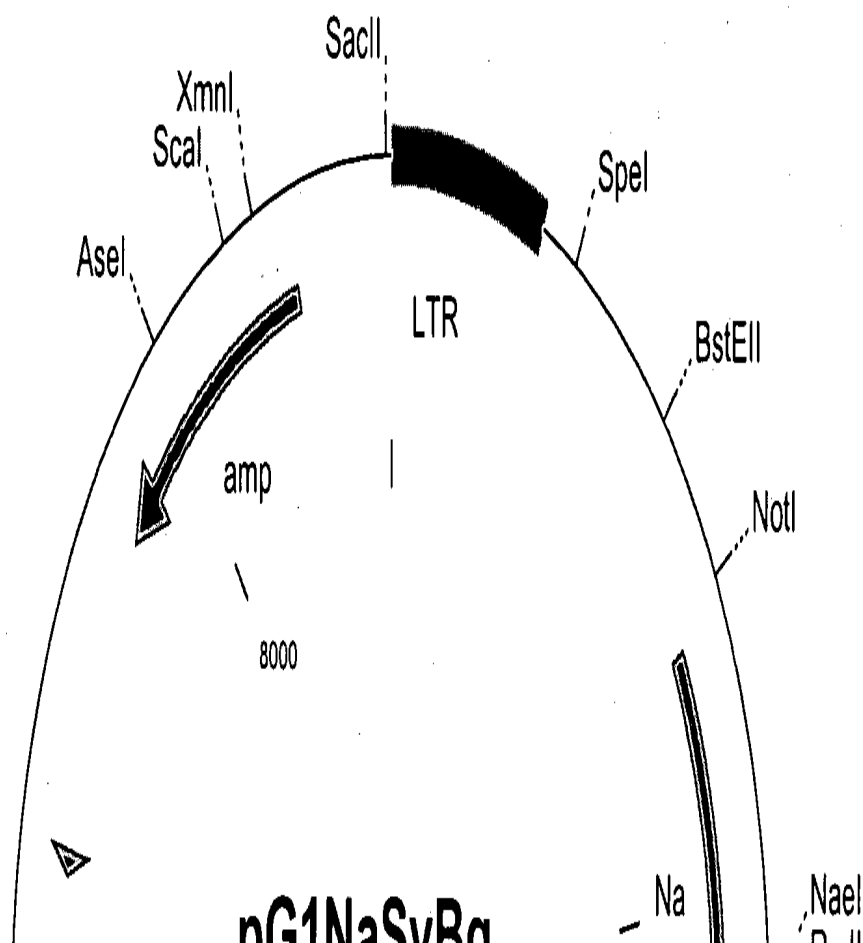


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Application #: Not Yet Assigned
Title: NOVEL ONCOLYTIC ADENOVIRAL VECTOR
Inventor: ENNIST et al.
Docket #: 4-31704A/GTI
Attorney: GTI (302) 258-4619

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Figure 16. Schematic diagram of plasmid pG1NaSvBg.



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Figure 17. Sequence of the murine GM-CSF cDNA (Seq ID NO:7) and protein (Seq ID NO:8).

7878 TTCCGGACAG ACCTCAATAA CTCTGTTTAC CAGAACAGGA GGTGAGCTTA
7928 GAAAACCCCTT AGGGTATTAG GCCAAAGGCG CAGCTACTGT GGGGTTTATG
7978 AACAAATTCAA GCAACTCTAC GGGCTATTCT AATTCAGGTT TCTCTAGCCG
8028 GGCTGCAGGA ATTCGATGGC CGCTACCTAC AATGGCCCCAC GAGAGAAAGG
M A H E R K
8078 CTAAGGTCCT GAGGAGGATG TGGCTGCAGA ATTTACTTTT CCTGGGCATT
A K V L R R M W L Q N L L F L G I
8128 GTGGTCTACA GCCTCTCAGC ACCCACCCGC TCACCCATCA CTGTCACCCG
V V Y S L S A P T R S P I T V T
8178 GCCTTGGAAG CATGTAGAGG CCATCAAAGA AGCCCTGAAC CTCCTGGATG
R P W K H V E A I K E A L N L L D
8228 ACATGCCTGT CACATTGAAT GAAGAGGTAG AAGTCGTCTC TAACGAGTTC
D M P V T L N E E V E V V S N E F
8278 TCCTTCAAGA AGCTAACATG TGTGCAGACC CGCCTGAAGA TATTCGAGCA
S F K K L T C V Q T R L K I F E
8328 GGGTCTACGG GGCAATTTCA CCAAACCTCAA GGGCGCCTTG AACATGACAG
Q G L R G N F T K L K G A L N M T
8378 CCAGCTACTA CCAGACATAC TGCCCCCCAA CTCCGGAAAC GGAAGTGAA
A S Y Y Q T Y C P P T P E T D C E
8428 ACACAAGTTA CCACCTATGC GGATTTTCATA GACAGCCTTA AAACCTTTCT
T Q V T T Y A D F I D S L K T F
8478 GACTGATATC CCCTTTGAAT GCAAAAAACC AGTCCAAAAA TGAGGAAGCC
L T D I P F E C K K P V Q K -
8528 CAGGCCAGCT CTGAATCCAG CTTCTCAGAC TGCTGCTTTT GTGCCTGCGT
8578 AATGAGCCAG GAACTCGGAA TTTCTGCCTT AAAGGGACCA AGAGATGTGG
8628 CACAGGTAGT CGAATCAAGC TTATCGATAC CGTCGACCTC GACTAGATAA
8678 CTTCTGTATAA TGTATGCTAT ACGAAGTTAT GCTAGAAATG GACGGAATTA
8728 TTACAGAGCA GCGCCTGCTA GAAAGACGCA GGGCAGCGGC CGAGCAACAG
8778 CGCATGAATC AAGAGCTCCA AGACATGGTT AACTTGCACC AGTGCAAAA 8826

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Figure 18. Pathway used to generate pAr6pAE2fmGmF plasmid.

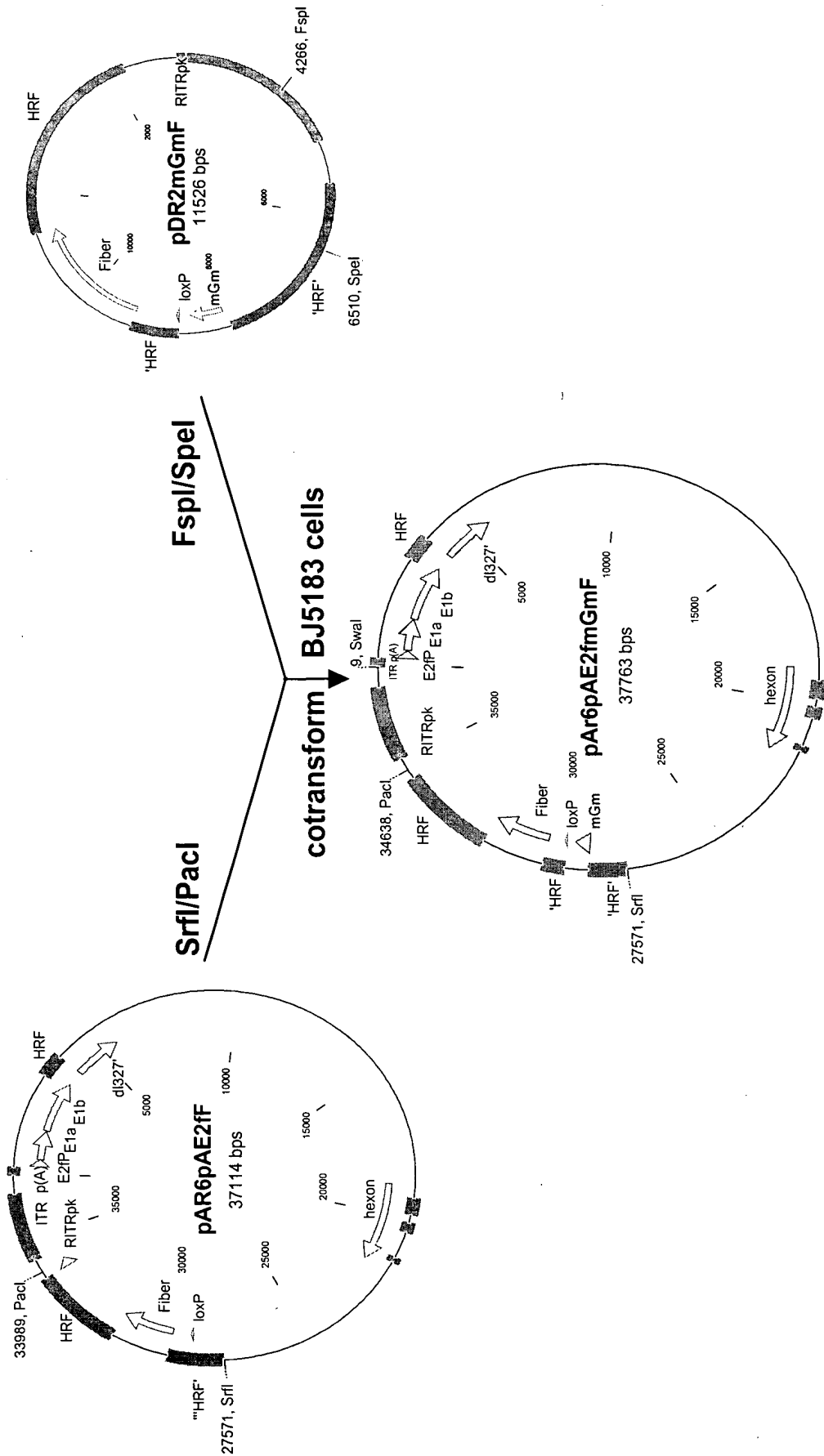


Figure 19. MTS assay of oncolytic vectors on different tumor cell lines.

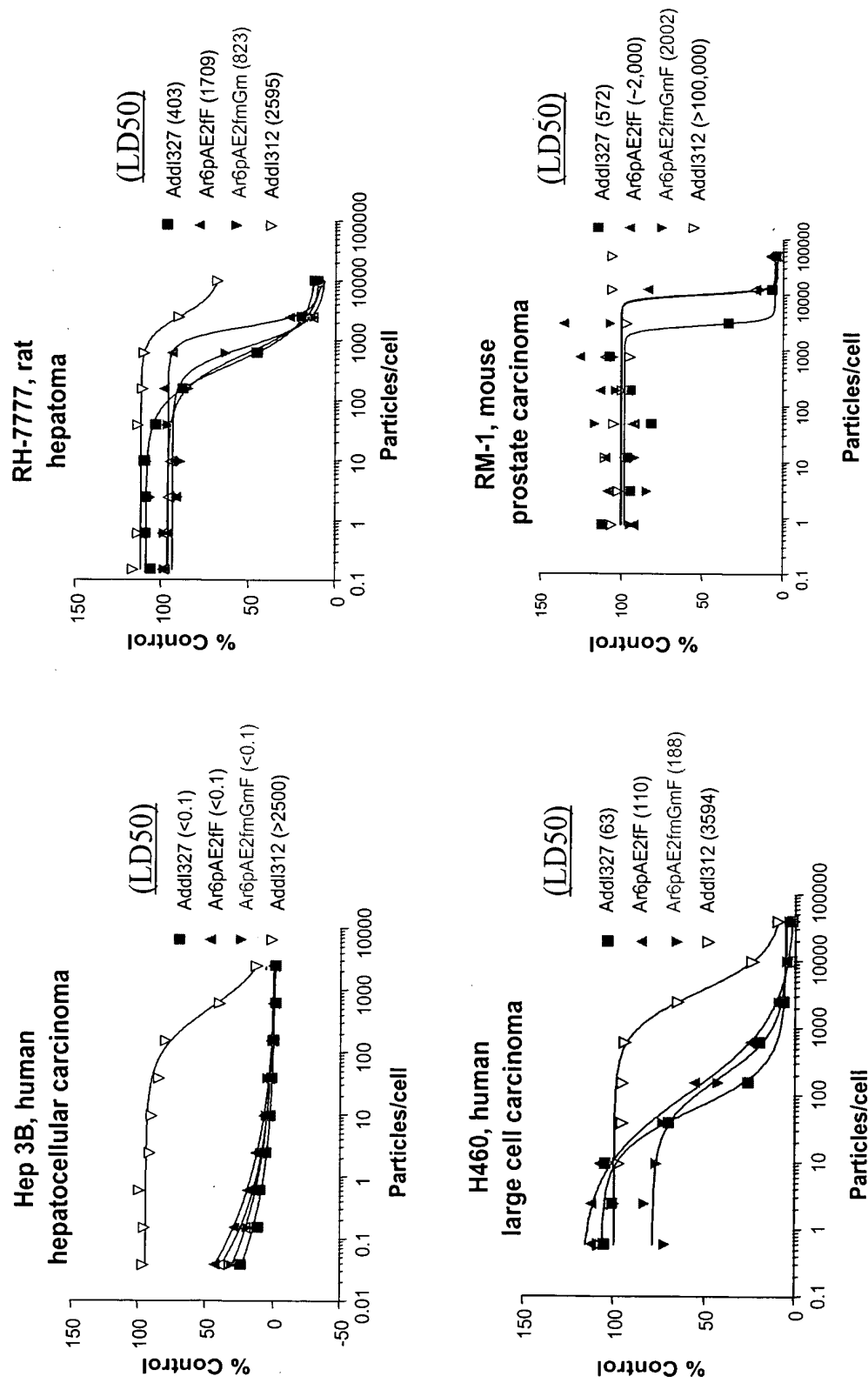


Figure 20. Sequence of the human GM-CSF cDNA (Seq ID NO:19) and protein (Seq ID NO:20).

28536 TATTAGGCCA AAGGCGCAGC TACTGTGGGG TTTATGAACA ATTCAAGCAA
28586 CTCTACGGGC TATTCTAATT CAGGTTTCTC TAGGATCTTT CCGCAGCAGC

28636 CGCCACCATG TGGCTGCAGA GCCTGCTGCT CTTGGGCACT GTGGCCTGCA
M W L Q S L L L L G T V A C

28686 GCATCTCTGC ACCCGCCCCG CCGCCAGCC CCAGCACGCA GCCCTGGGAG
S I S A P A R S P S P S T Q P W E

28736 CATGTGAATG CCATCCAGGA GGCCCGGCGT CTCCTGAACC TGAGTAGAGA
H V N A I Q E A R R L L N L S R

28786 CACTGCTGCT GAGATGAATG AAACAGTAGA AGTCATCTCA GAAATGTTTG
D T A A E M N E T V E V I S E M F

28836 ACCTCCAGGA GCCGACCTGC CTACAGACCC GCCTGGAGCT GTACAAGCAG
D L Q E P T C L Q T R L E L Y K Q

28886 GGCCTGCGGG GCAGCCTCAC CAAGCTCAAG GGCCCTTGA CCATGATGGC
G L R G S L T K L K G P L T M M

28936 CAGCCACTAC AAGCAGCACT GCCCTCCAAC CCCGGAAACT TCCTGTGCAA
A S H Y K Q H C P P T P E T S C A

28986 CCCAGACTAT CACCTTTGAA AGTTTCAAAG AGAACCTGAA GGA CTTTCTG
T Q T I T F E S F K E N L K D F L

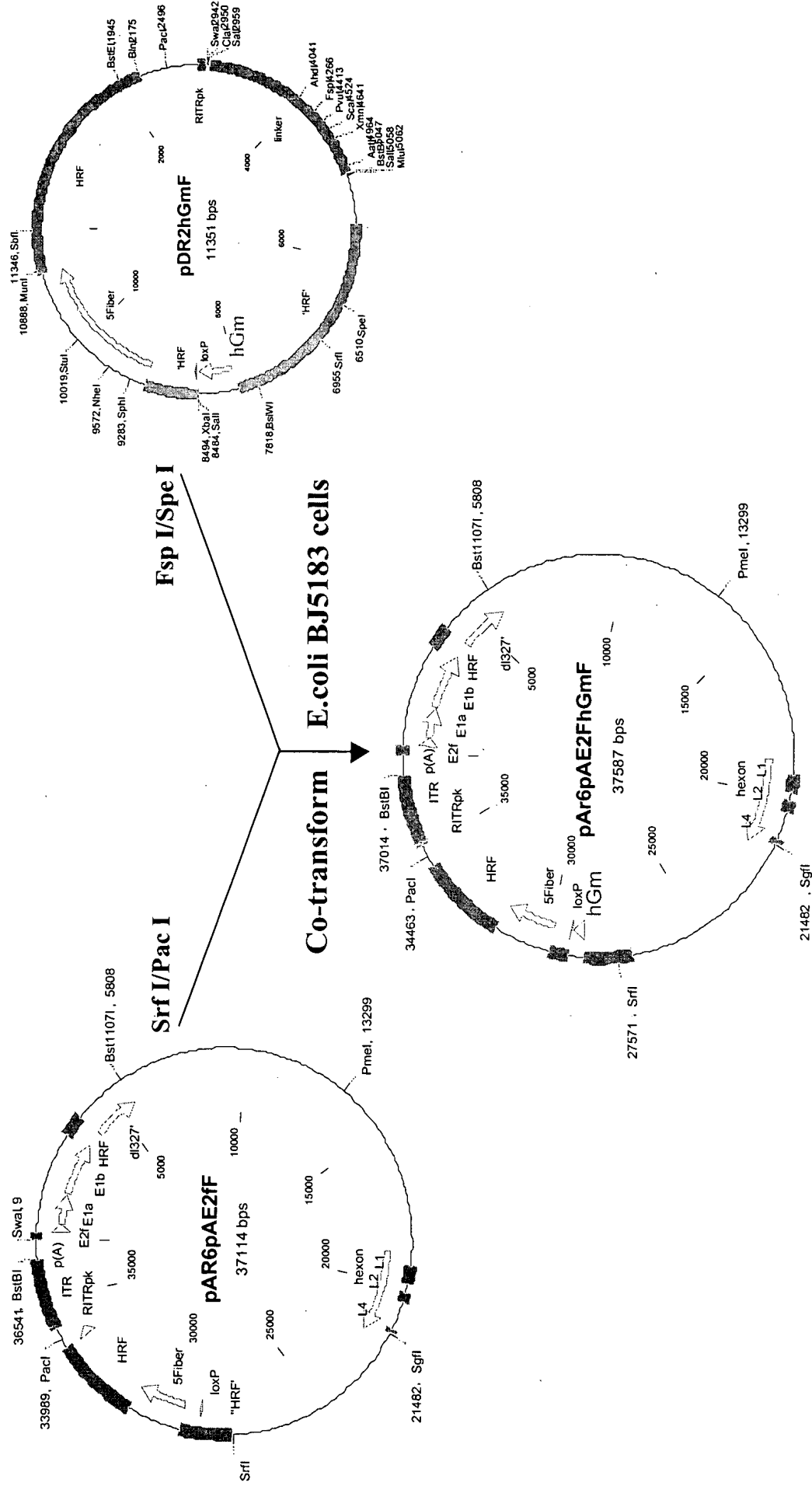
29036 CTTGTCATCC CCTTTGACTG CTGGGAGCCA GTCCAGGAGT GAGTCGACAA
L V I P F D C W E P V Q E -

29086 GCTCTAGATA ACTTCGTATA ATGTATGCTA TACGAAGTTA TGCTAGAAAT
29136 GGACGGAATT ATTACAGAGC AGCGCCTGCT AGAAAGACGC AGGGCAGCGG
29186 CCGAGCAACA GCGCATGAAT CAAGAGCTCC AAGACATGGT TAACTTGCAC
29236 CAGTGCAAAA GGGGTATCTT TTGTCTGGTA AAGCAGG 29273

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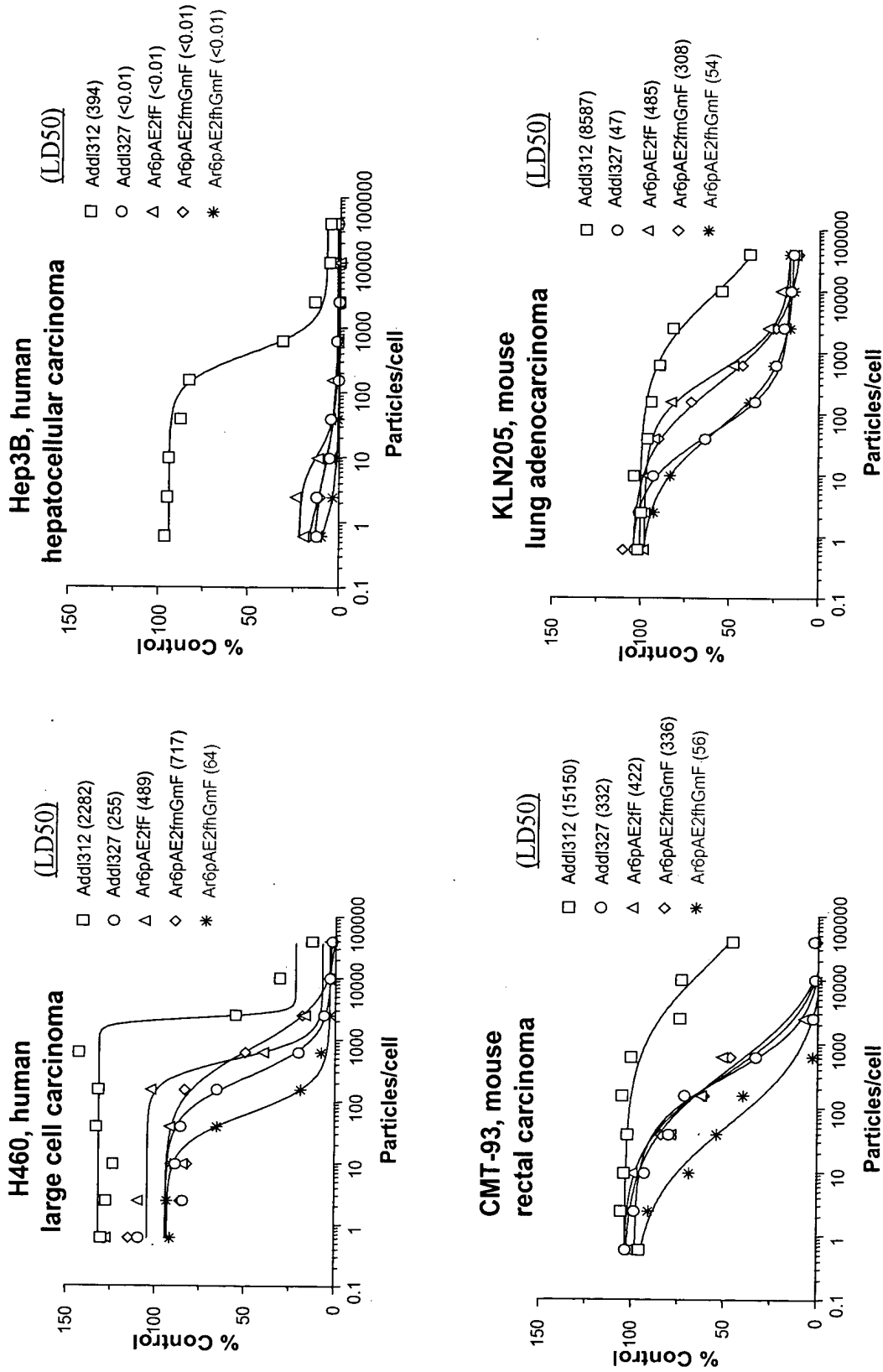
Figure 21. Pathway used to generate pAr6pAE2fhGmF plasmid.



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Figure 22. MTS assay of oncolytic vectors on different tumor cell lines.



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Figure 23. Efficacy of GM-CSF armed oncolytic vectors in H460 tumor model

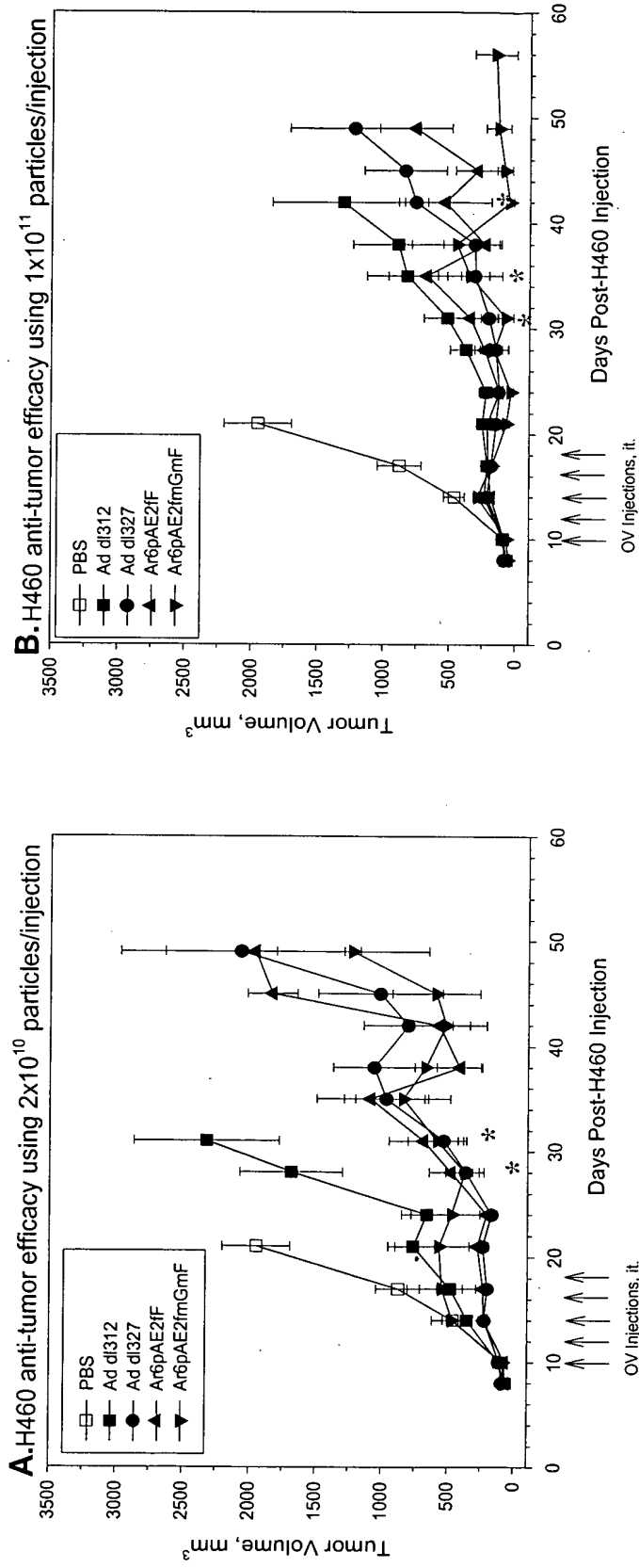


Figure 24. Efficacy of GM-CSF armed oncolytic vectors in Hep3B tumor model

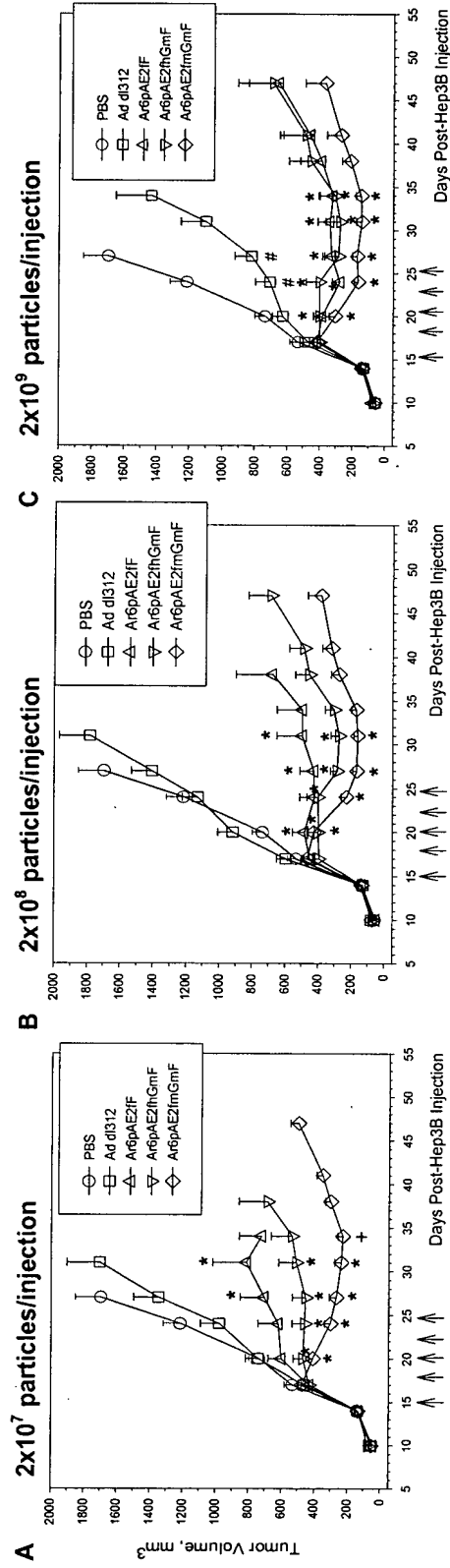


Figure 25. Schematic Diagram of PCR and Overlap PCR for Δ gp19 Donor Plasmids

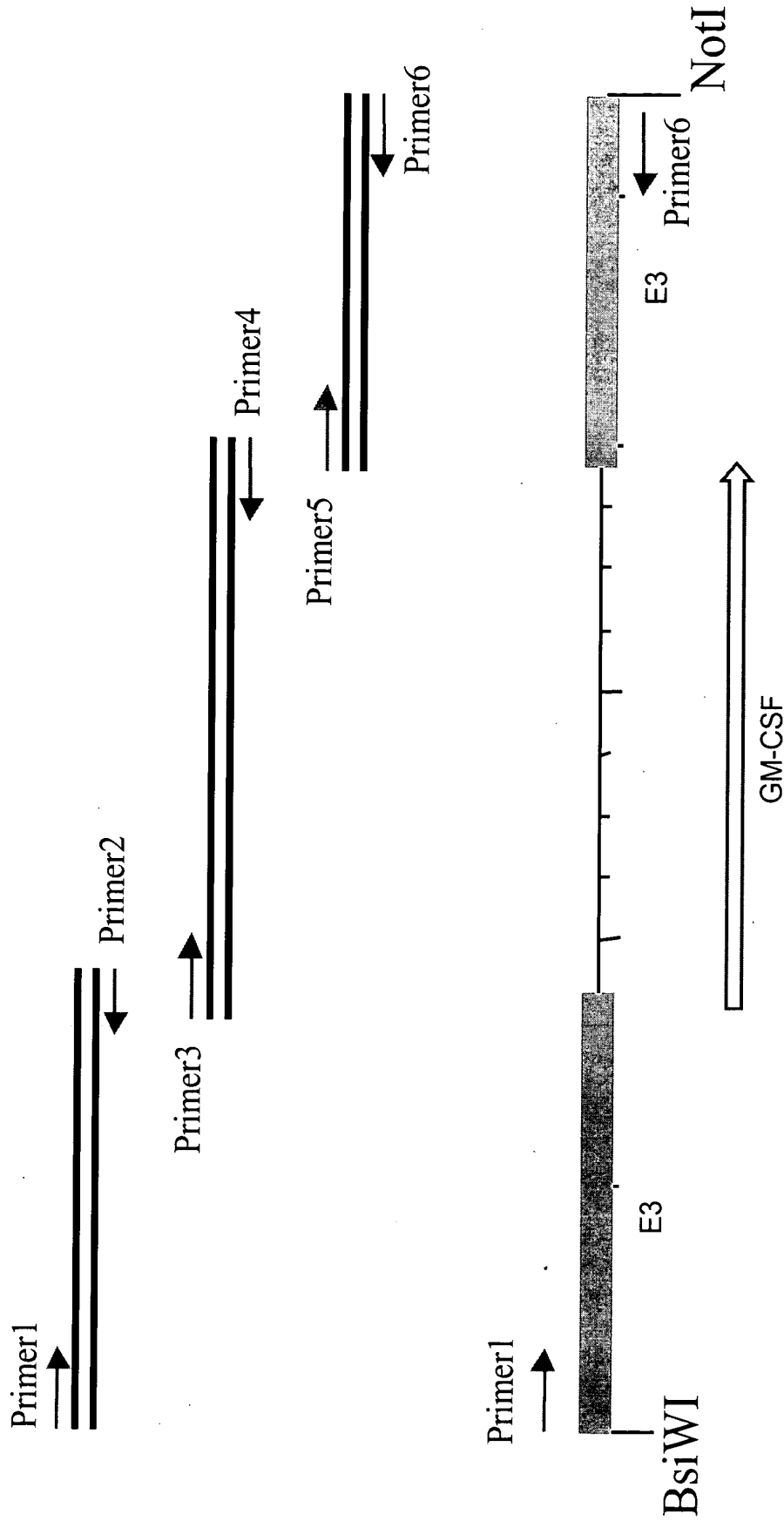
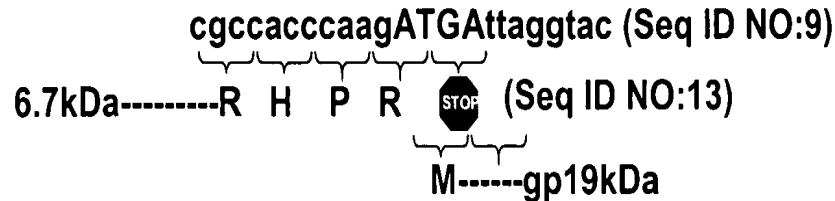
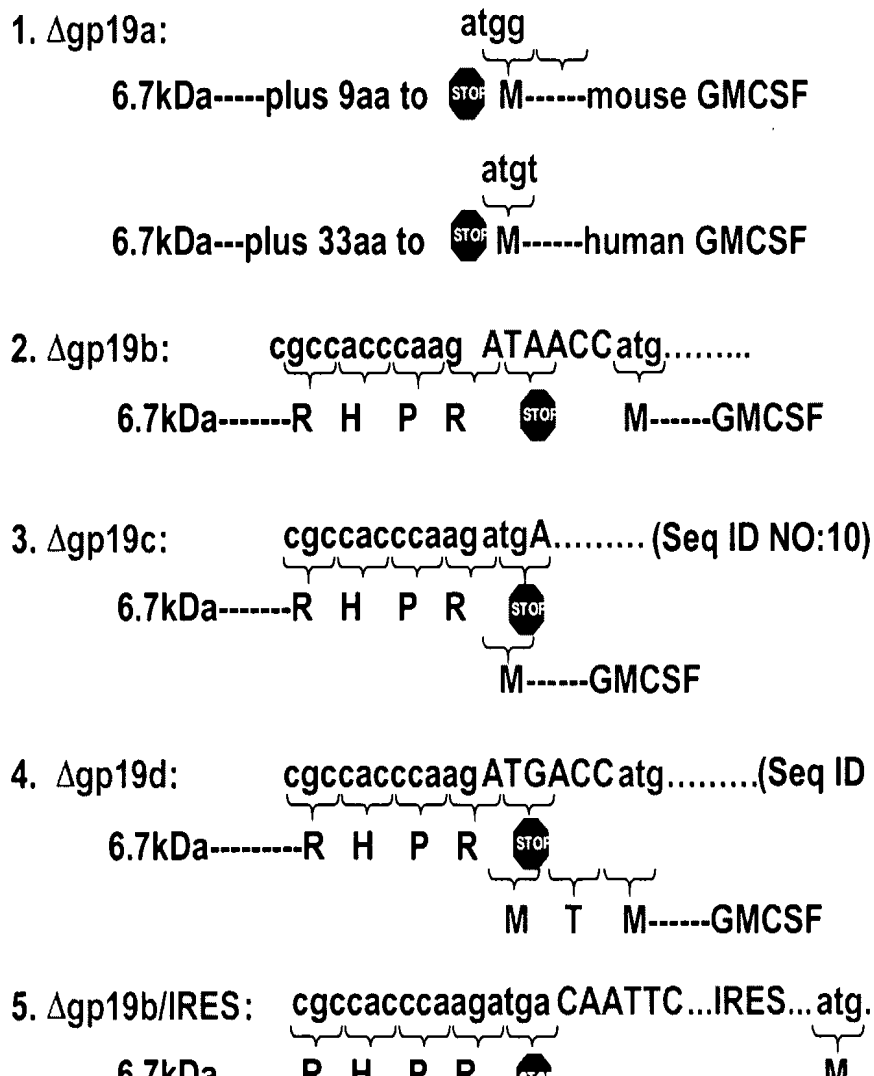


Figure 26. Schematic Diagram of \square gp19 Vectors

a. Sequence of native E3 region:



b. Sequence comparison of Δ gpl9 vectors at the junction between E3-6.7 and GM-CSF:



5. Δ gp19b/IRES: cgccaccaagatga CAATTC...IRES...atg.....(Seq ID NO:12)
 6.7kDa P H P P M CMCSE

Figure 27a. Pathway Used to Generate the pAr6pAE2f(E3+, mGm, Dg19b)F Large Plasmid

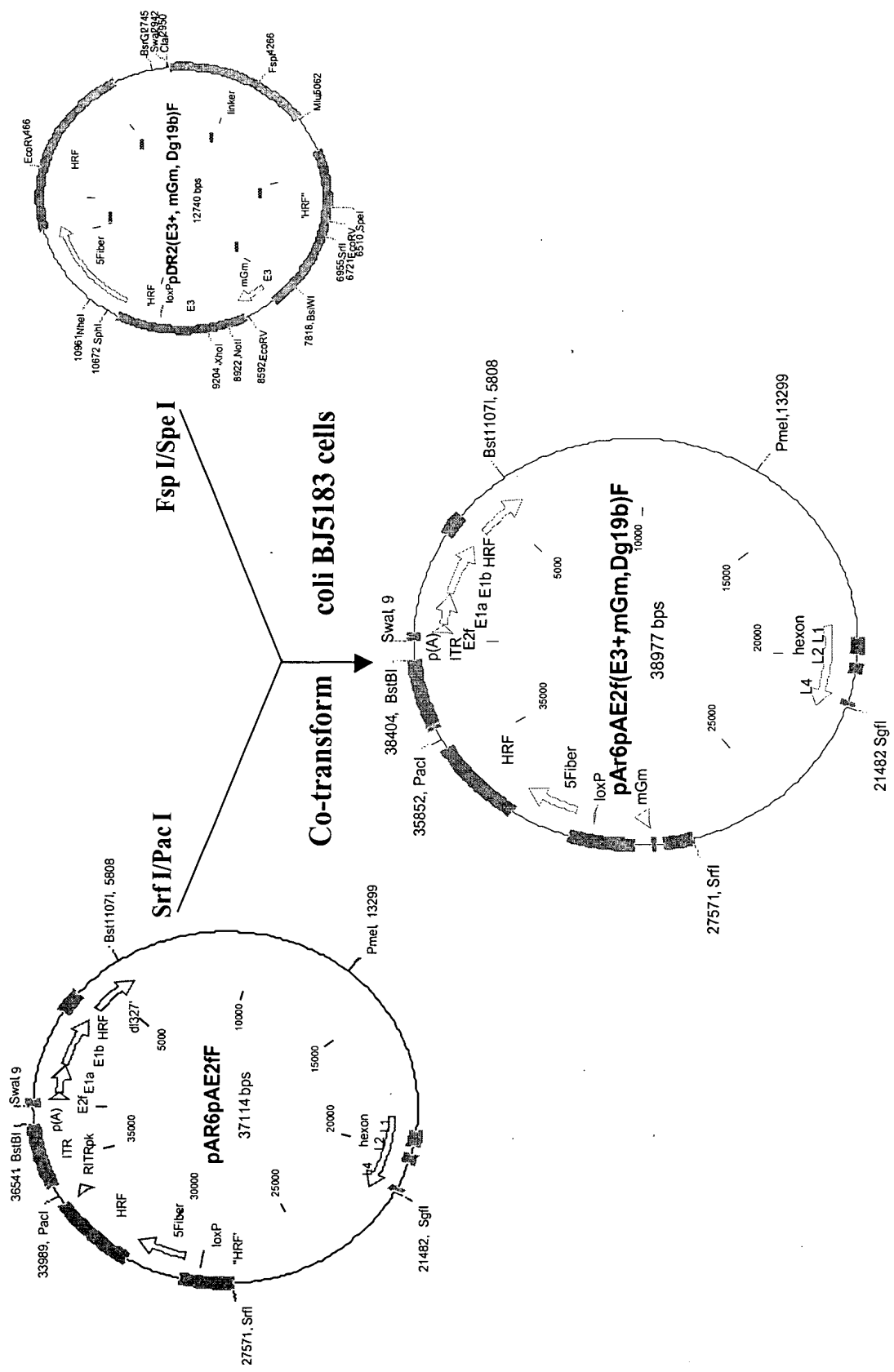
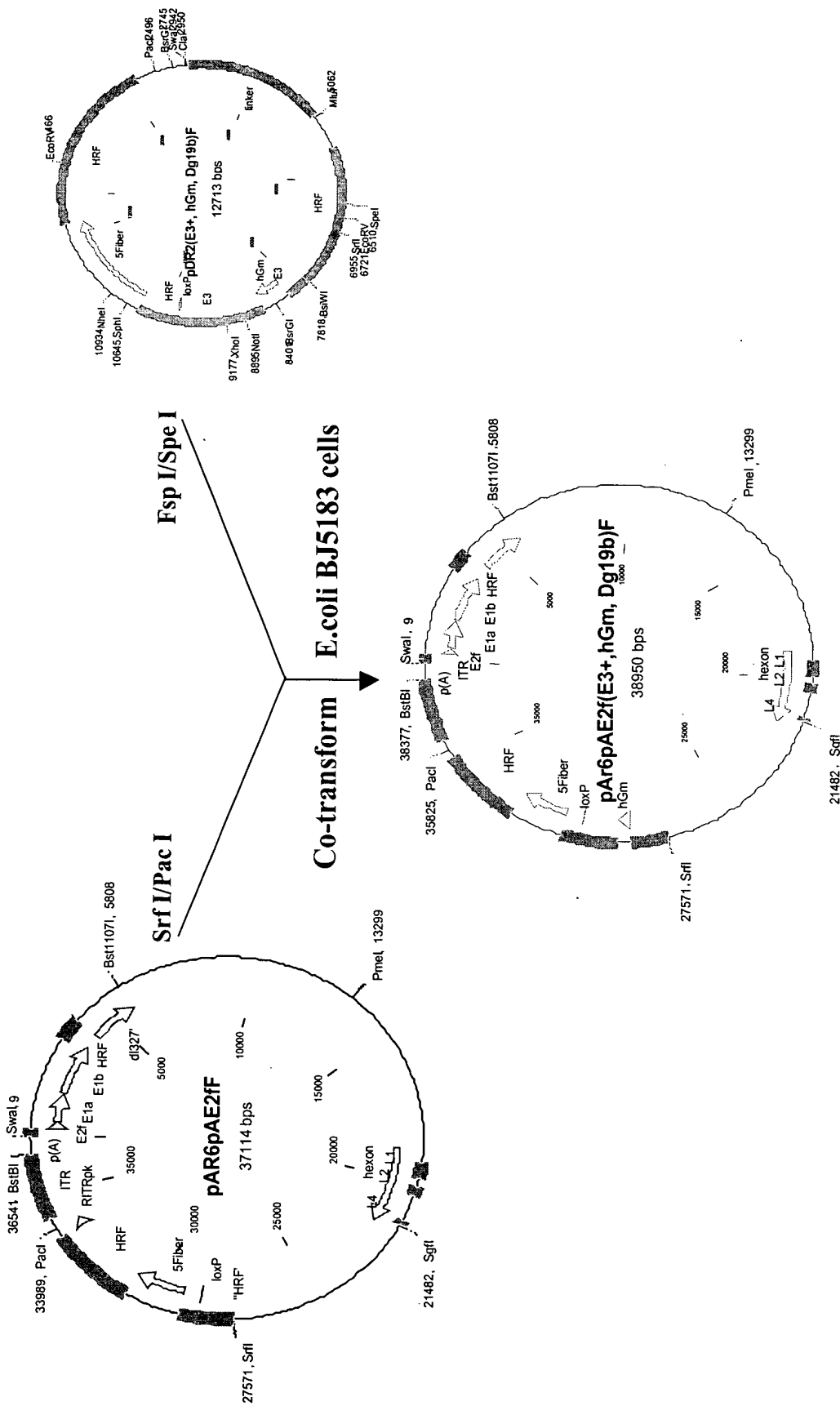


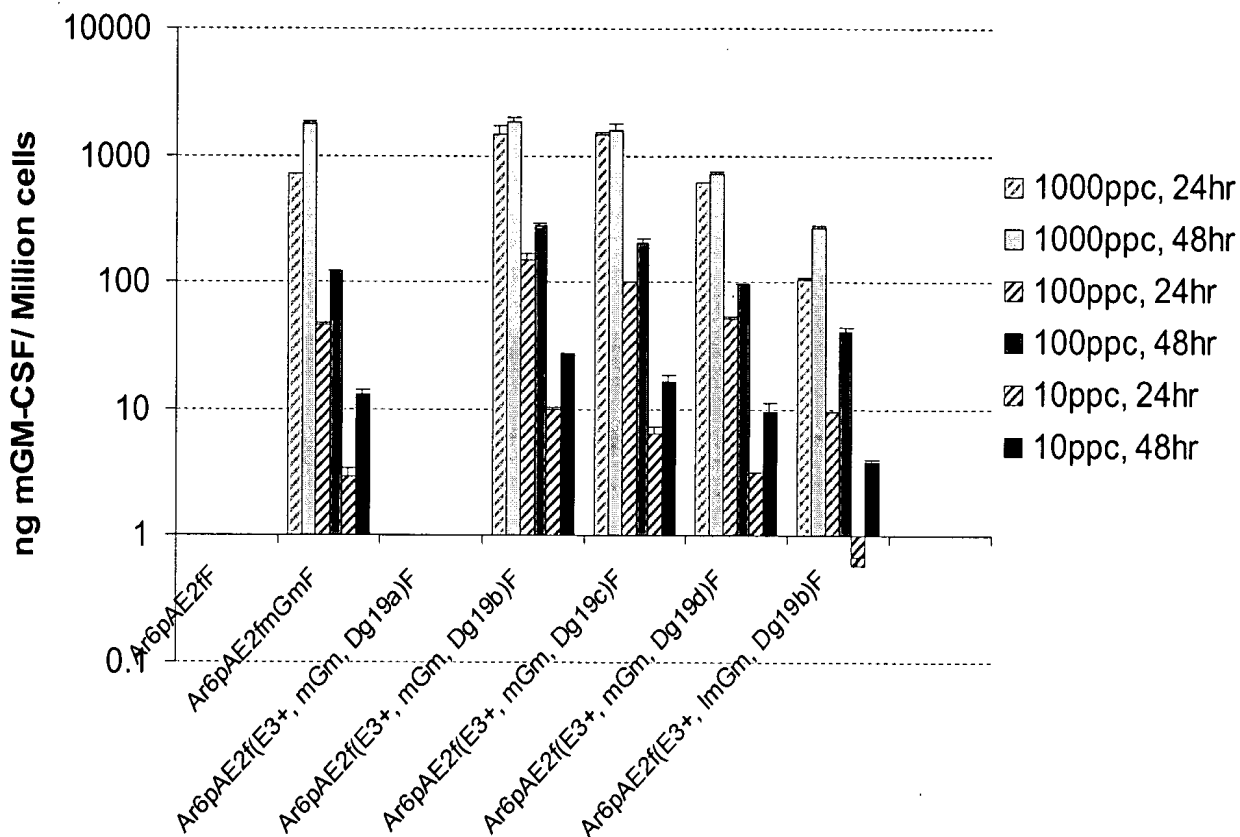
Figure 27b. Pathway Used to Generate the pAr6pAE2f(E3+,hGm,Dg19b)F Large Plasmid



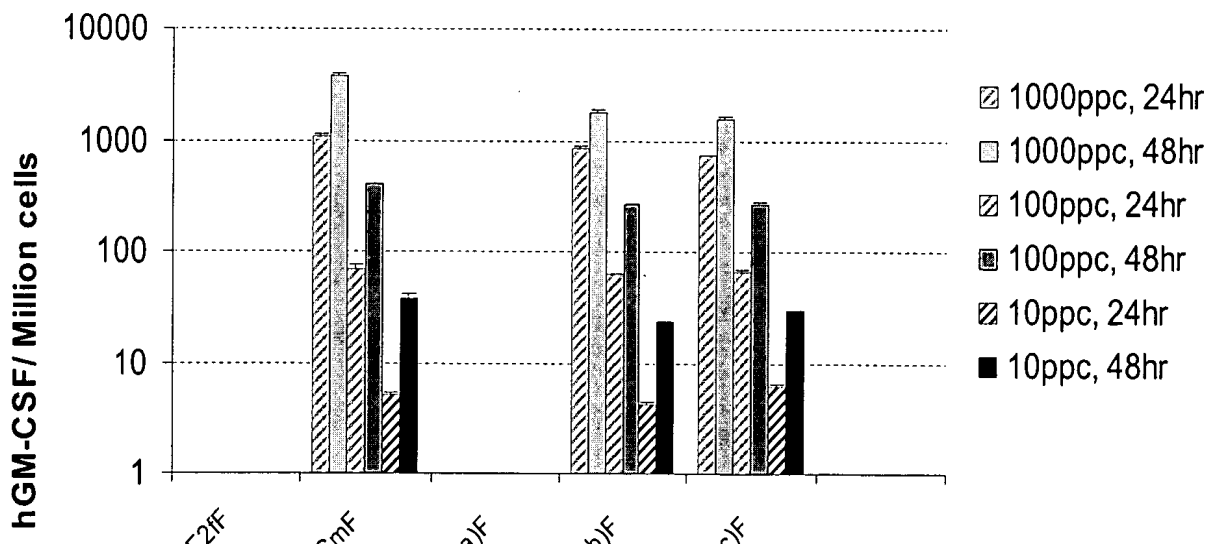
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Figure 29. GM-CSF Expression Mediated by Δ gp19 GM-CSF Vectors in Infected H460 Cells Detected by ELISA

a. Mouse GM-CSF expression in H460 cells



b. Human GM-CSF expression in H460 cells



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Figure 30. Anti-Tumor Activity of Oncolytic Adenoviruses (2×10^9 particles/injection) in the Hep3B Xenograft Subcutaneous Tumor Model

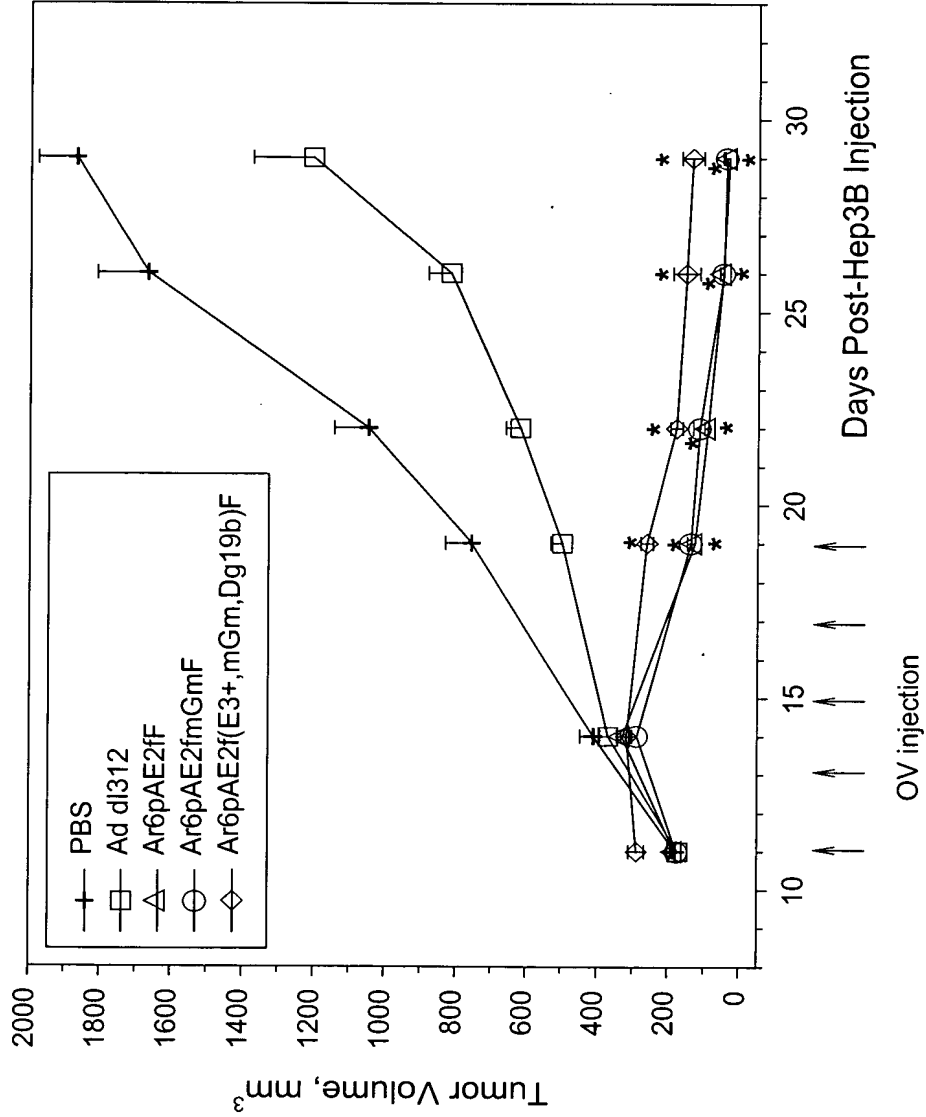
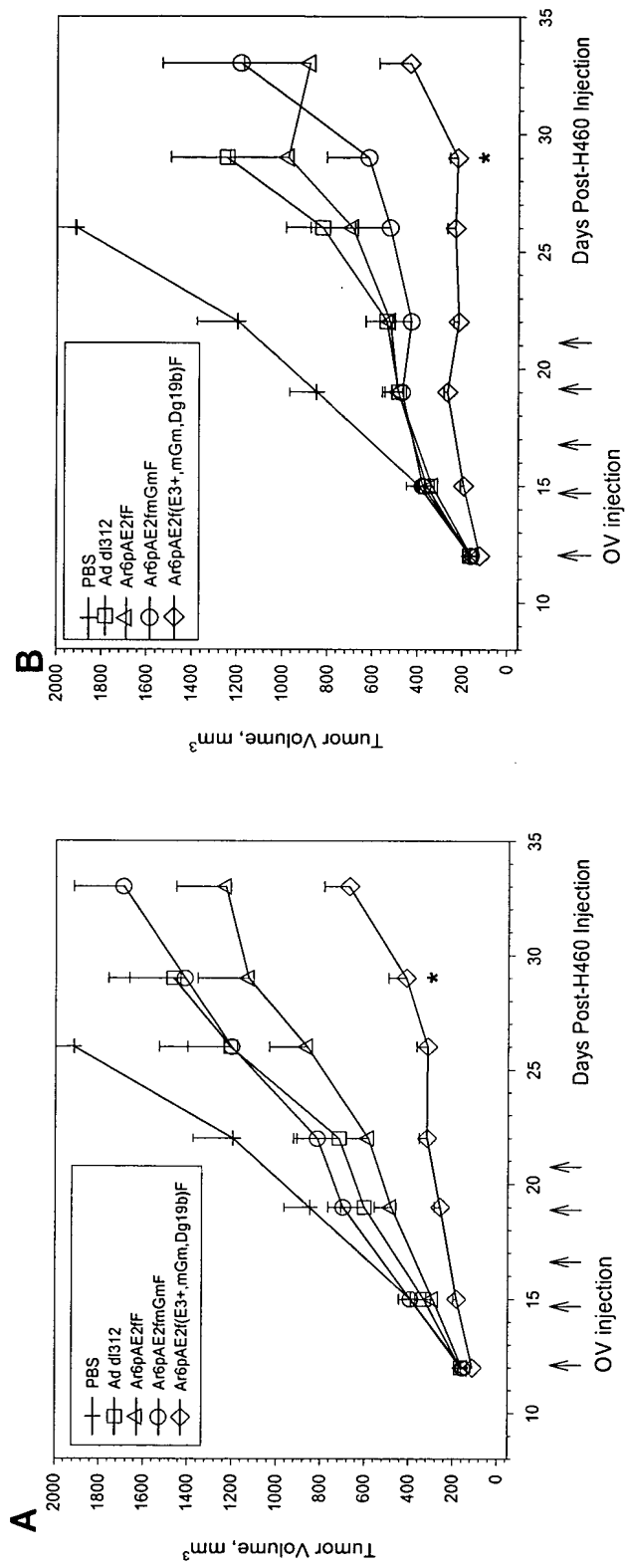


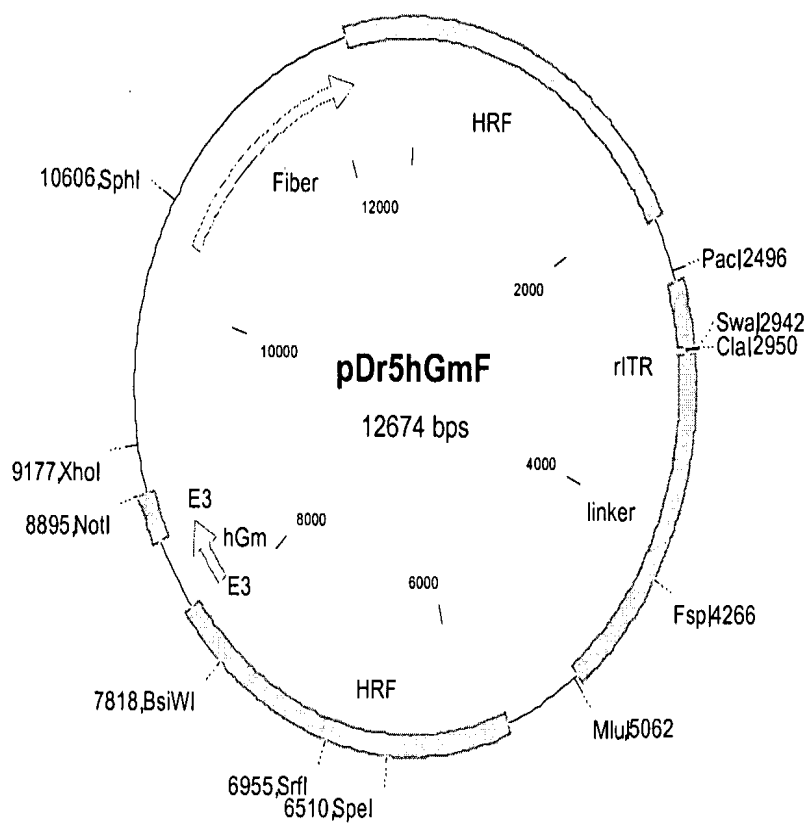
Figure 31. Anti-Tumor Activity of Oncolytic Adenoviruses in the H460 Xenograft Subcutaneous Tumor Model



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Figure 32. Schematic diagram of adenovirus pDr5hGmF and pDr5mGmF right donor plasmids.

A. pDr5hGmF



B. pDr5mGmF

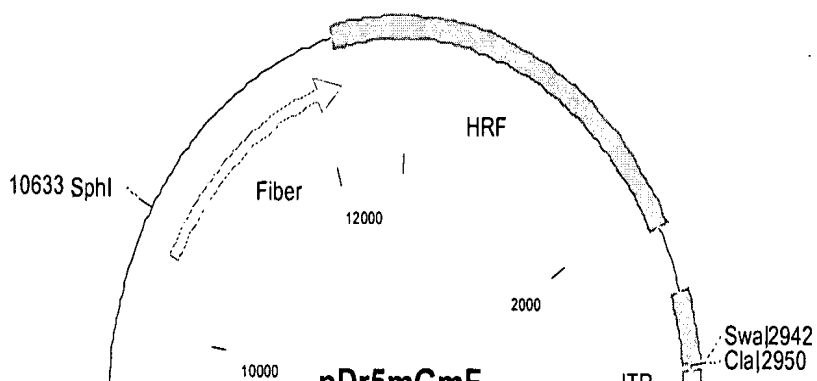
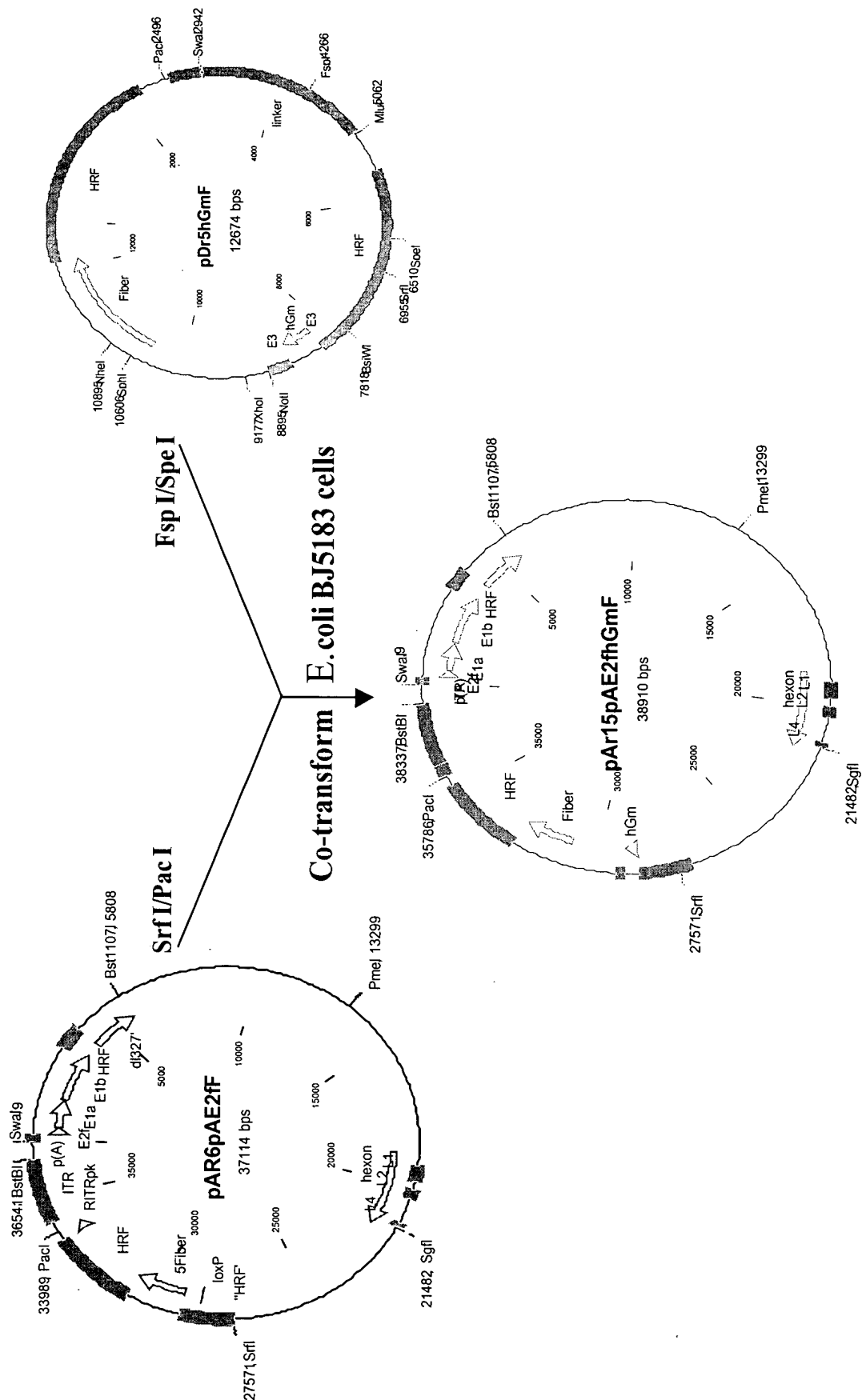


Figure 33. Pathway used to generate the pAr15pAE2fhGmF plasmid.



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Figure 34. Pathway used to generate the pAr15pAE2fmGmF plasmid.

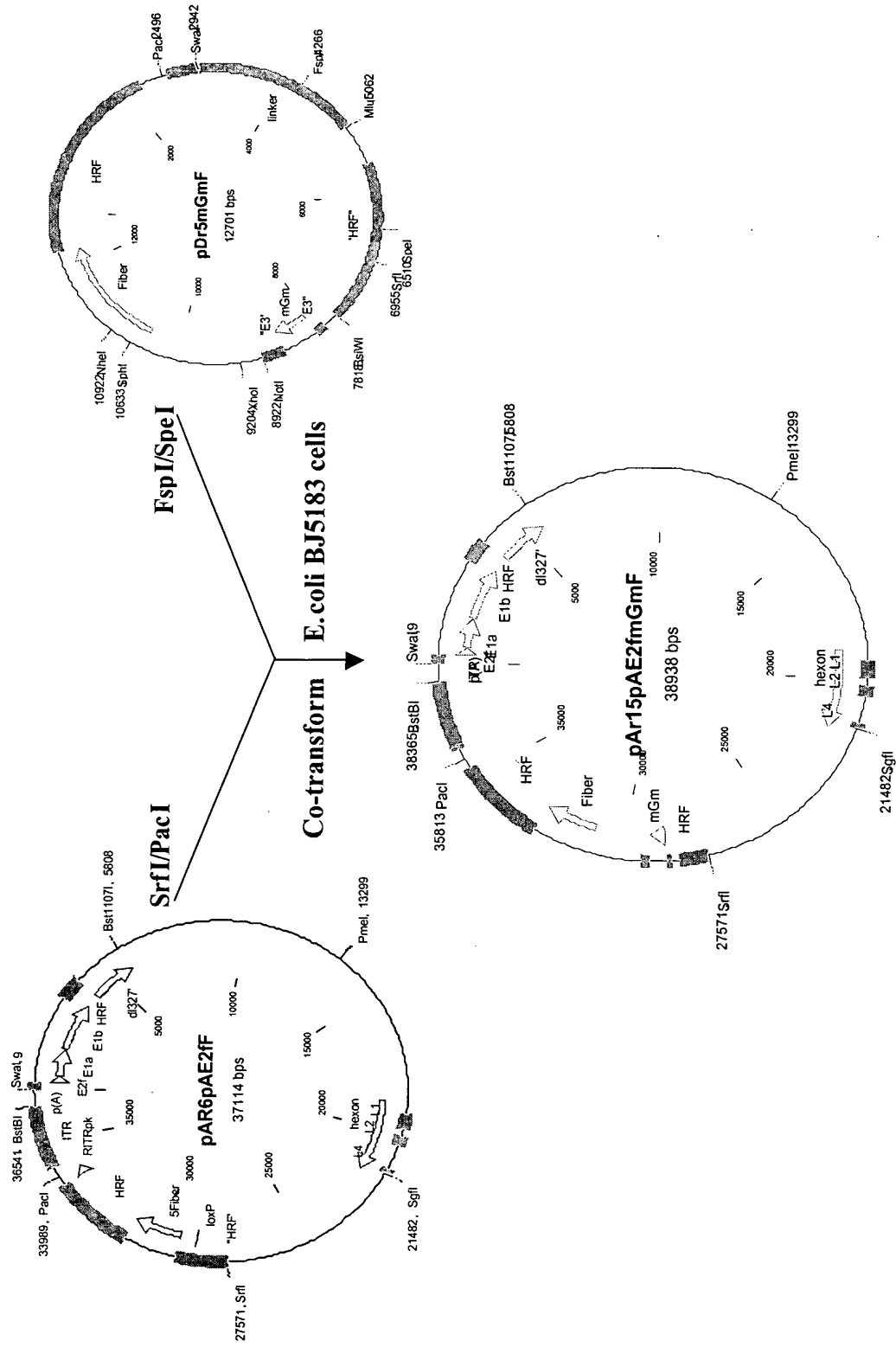
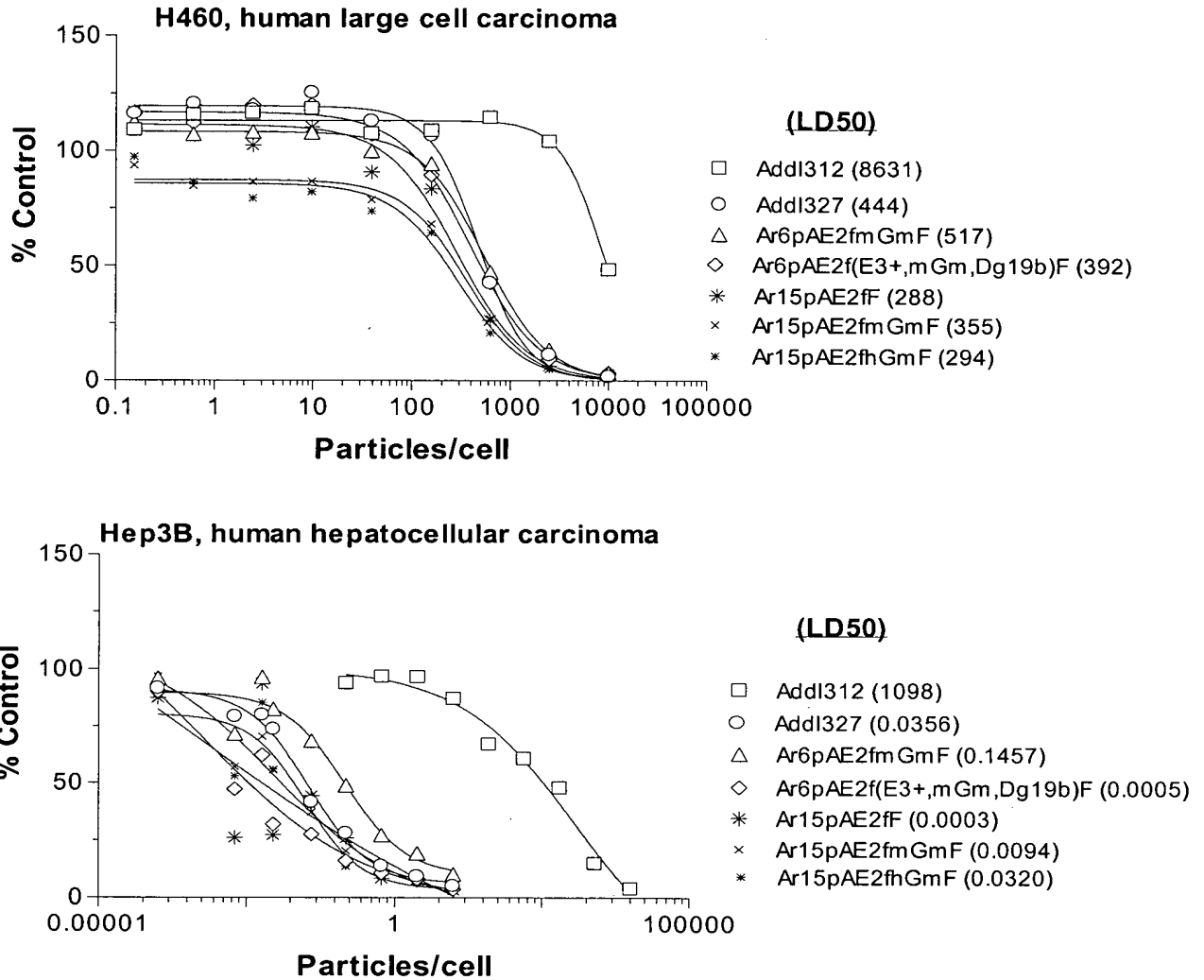


Figure 35. MTS assay of Ar15pAE2fhGmF and Ar15pAE2fmGmF vectors on H460 and Hep3B tumor cell lines.



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Figure 36. GM-CSF expression mediated by Ar15pAE2fhGmF and Ar15pAE2fmGmF vectors in infected H460 cells detected by ELISA.

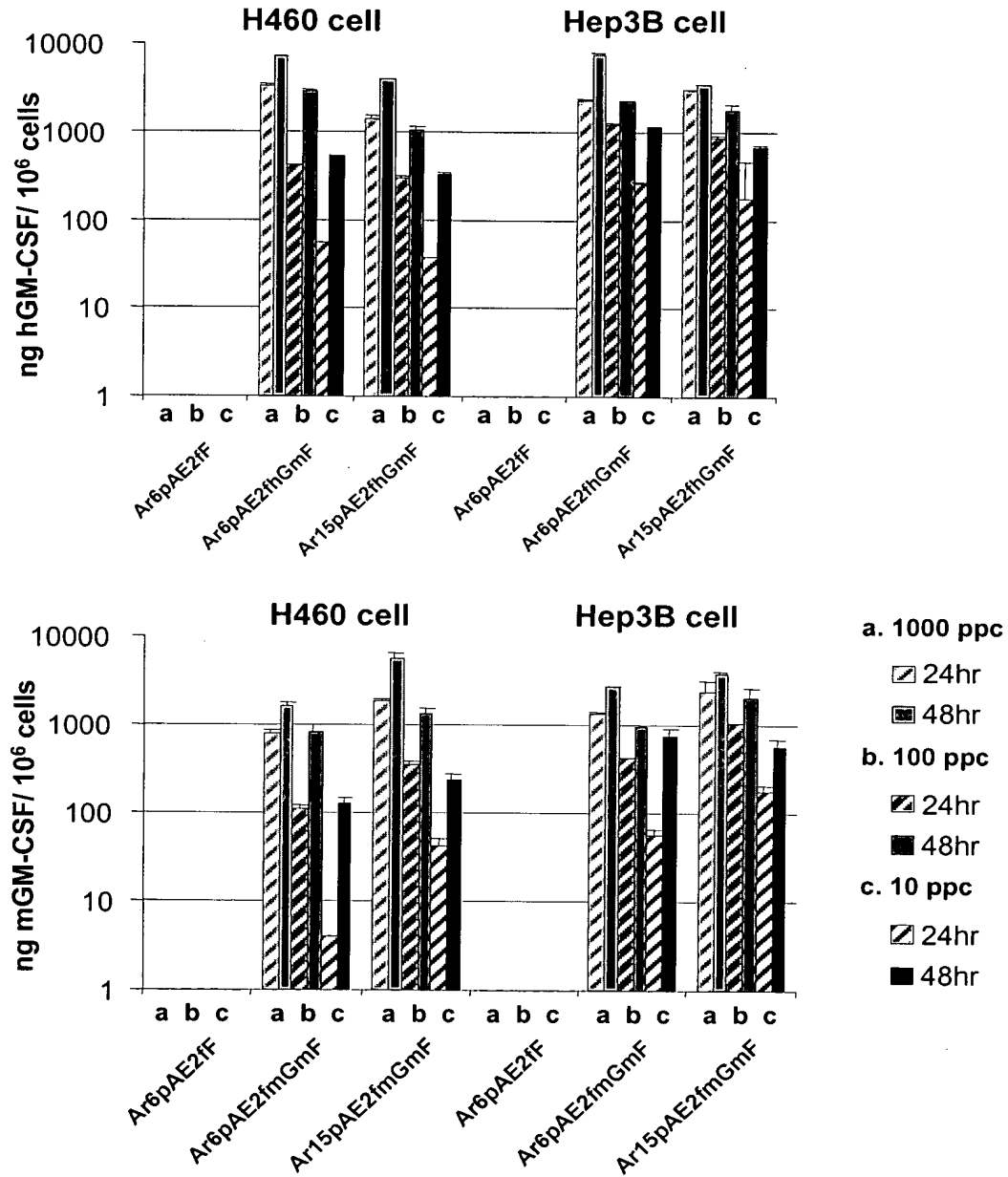
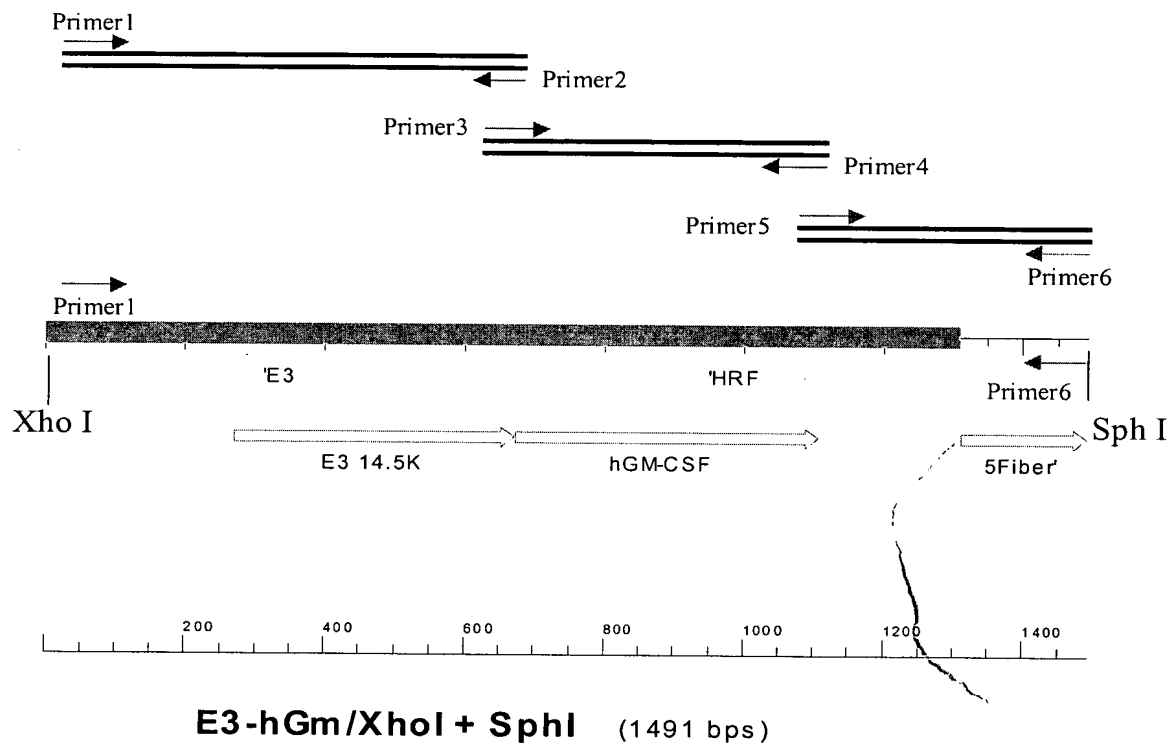


Figure 37. Schematic Diagram of PCR and Overlap PCR for Δ E3-14.7 plasmids





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Figure 39. Pathway Used to Generate the pAr16pAE2fhGmF Large Plasmid

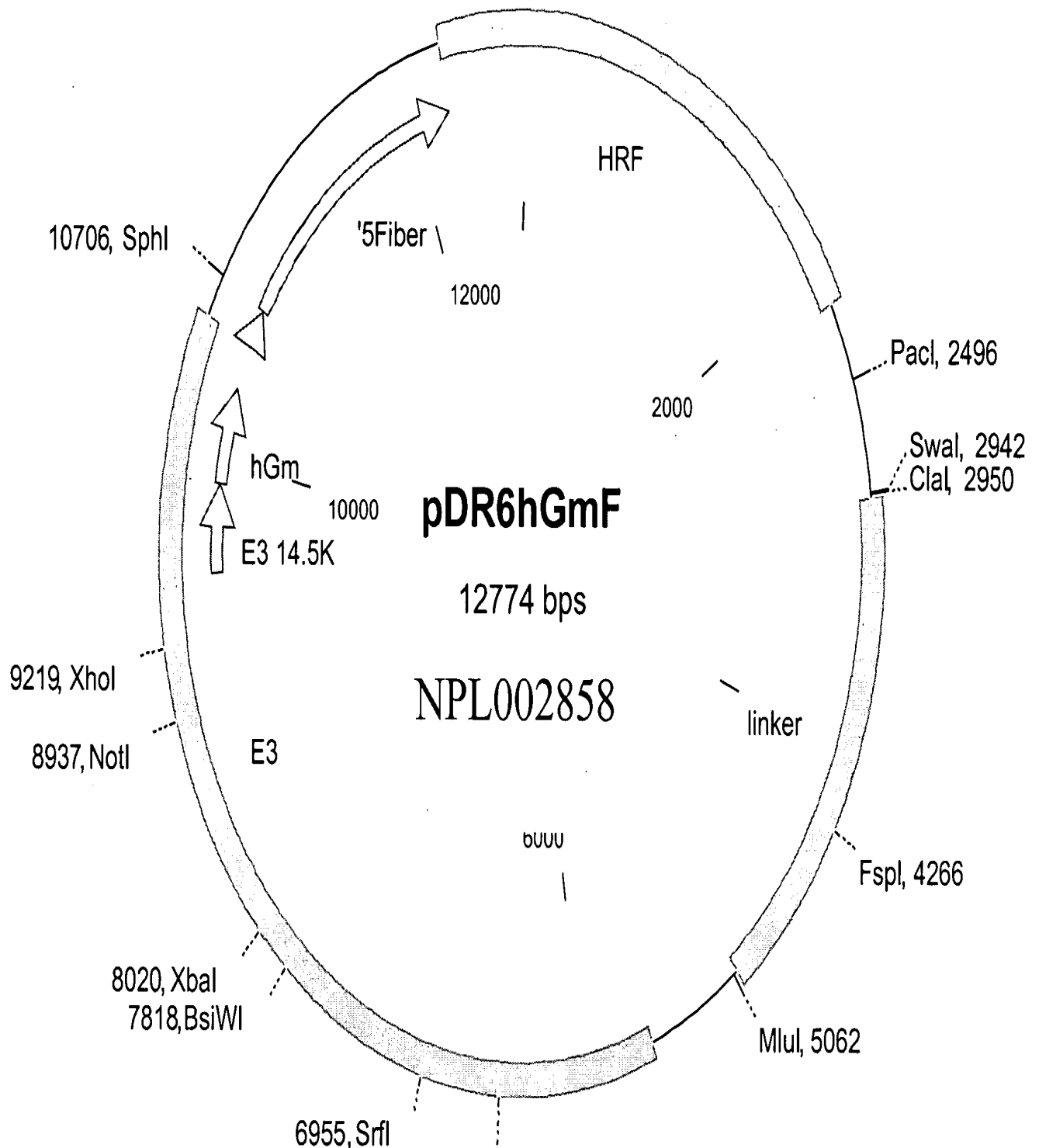


Figure 40. Pathway Used to Generate the pAr16pAE2fhGmF Large Plasmid

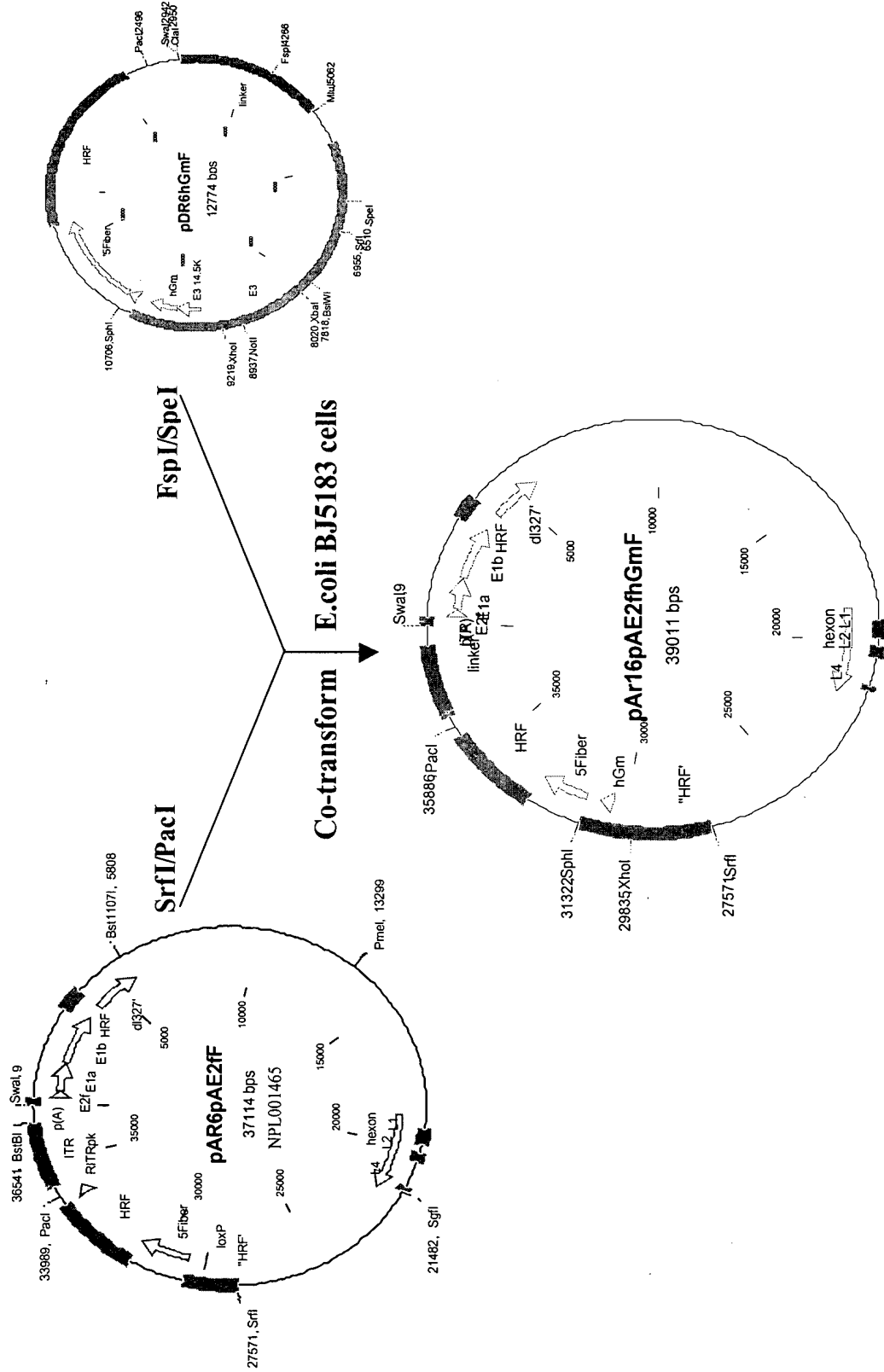
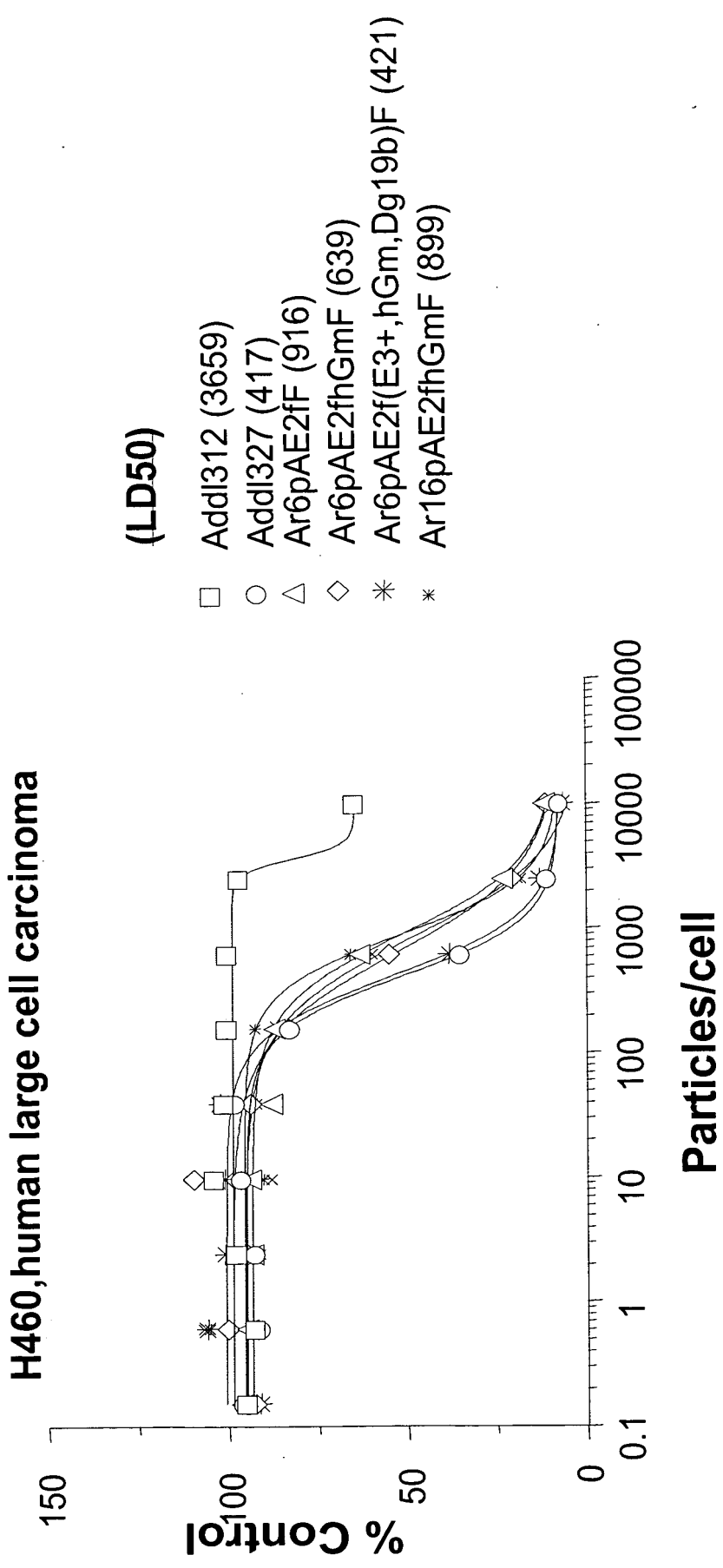
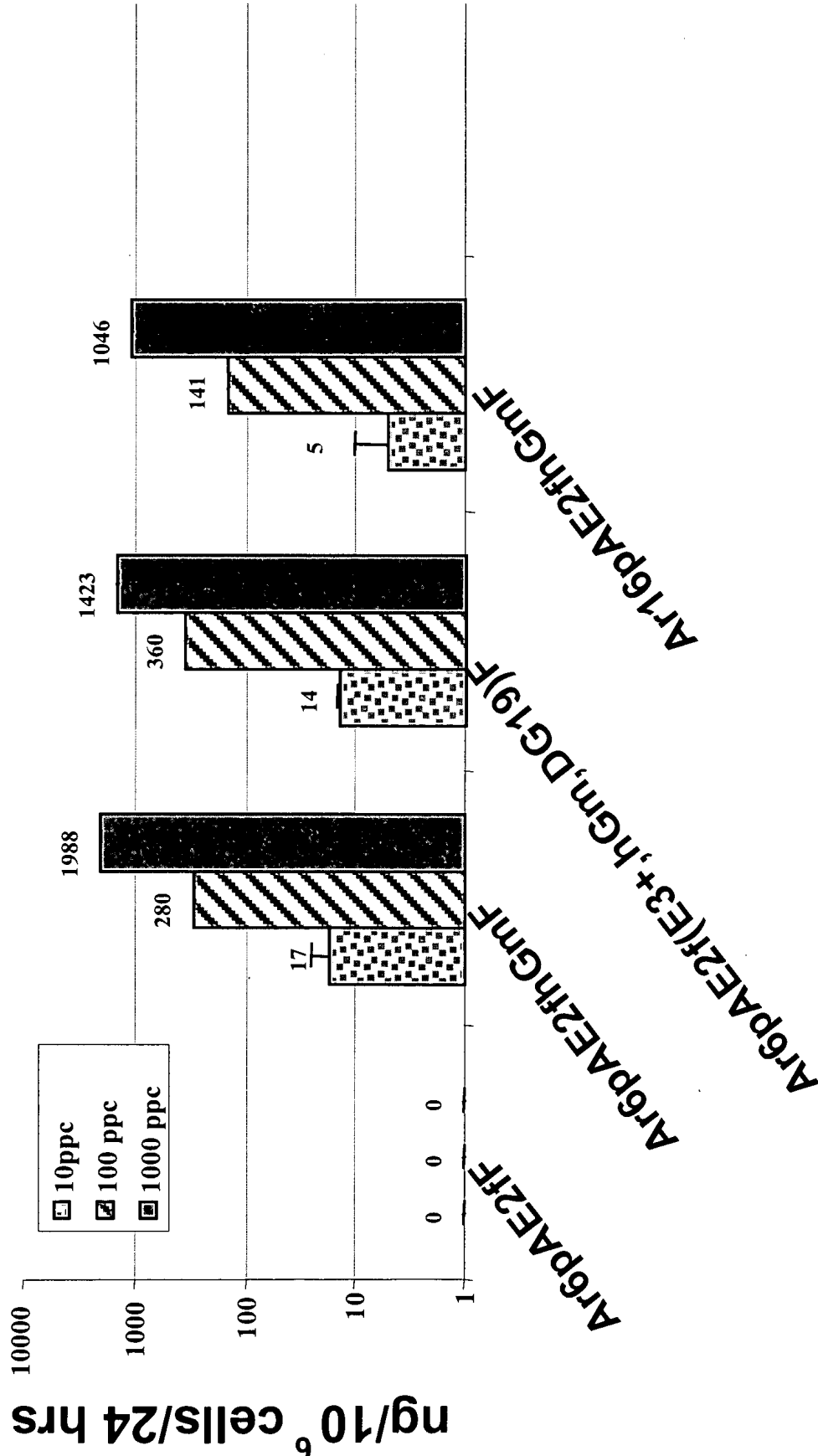


Figure 41. MTS Assay of Δ E3-14.7 hGM-CSF Vector on H460 Tumor Cell Line



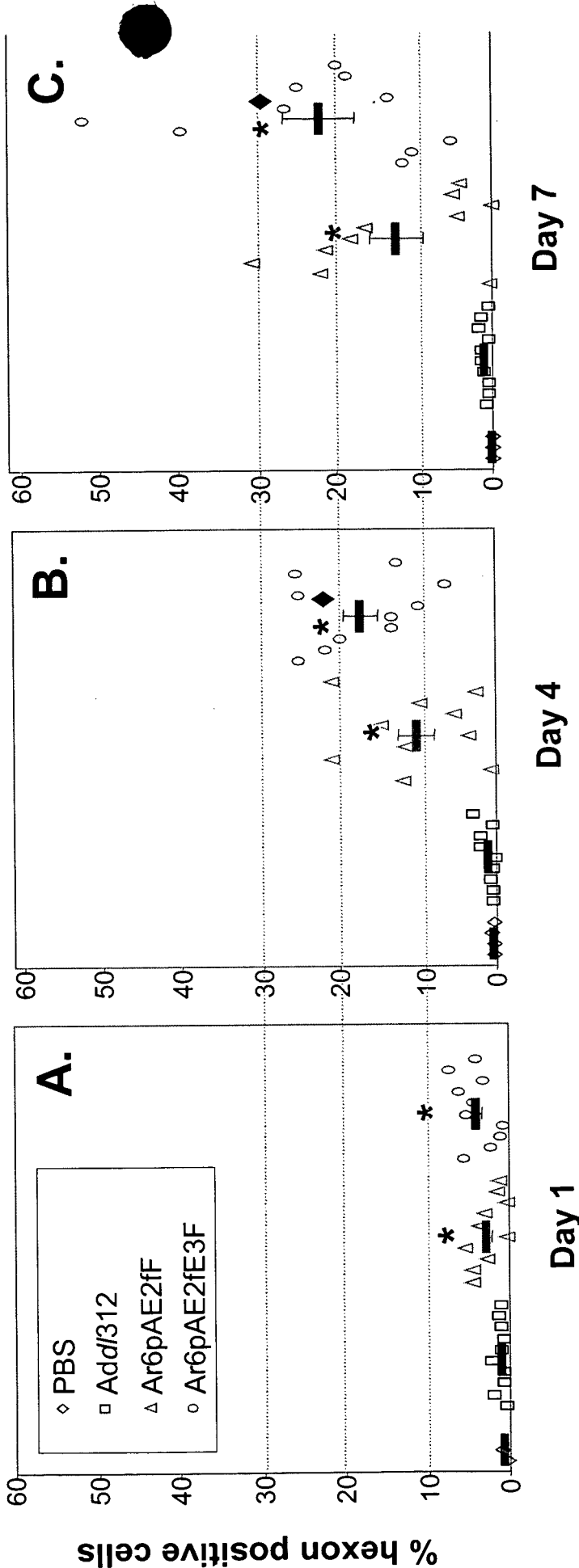
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Figure 42. GM-CSF Expression Mediated by Δ E3-14.7 hGM-CSF Vector (Ar16pAE2fhGmF) compared to Ar6pAE2fF, Ar6pAE2fF(E3+,hGm,Dg19)F in Infected H460 Cells 24 Hours Post-Infection



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Figure 43. Spread of adenoviruses in H460 xenograft tumors detected by FACS.

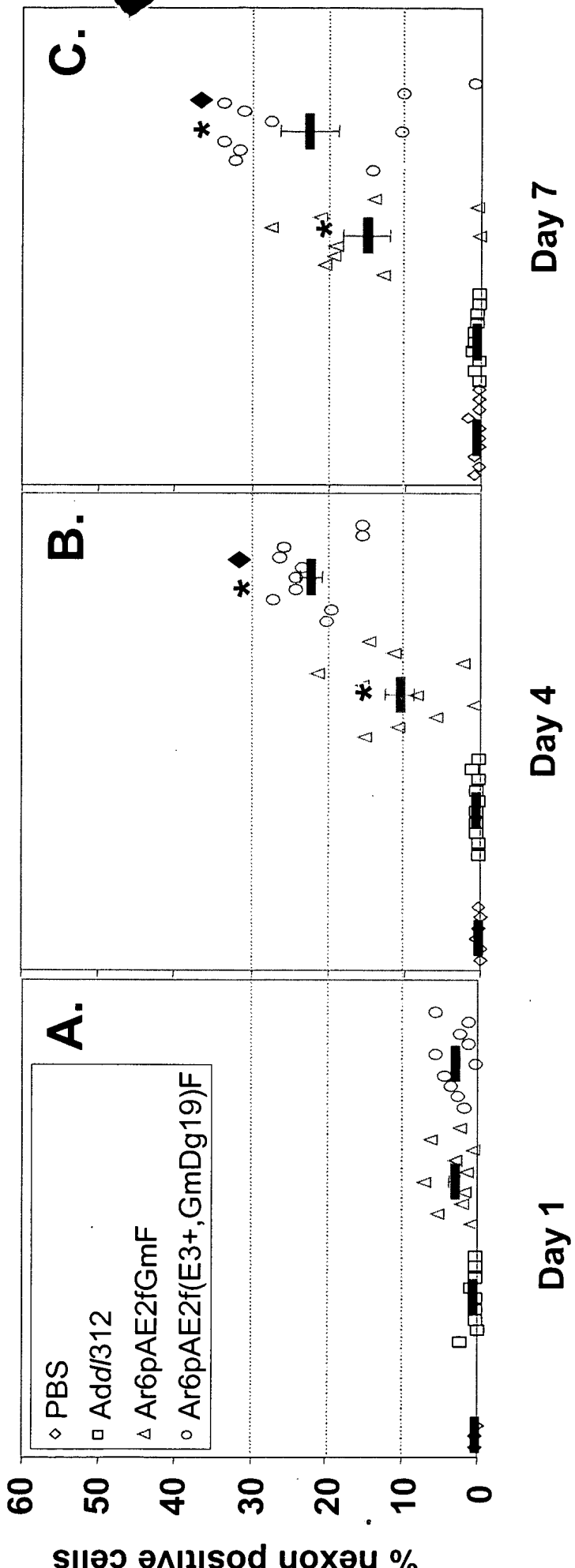


*: p<0.05 between Ar6pAE2fF and Ar6pAE2fE3F and Add1312, ANOVA
♦: p<0.05 between Ar6pAE2fF and Ar6pAE2fE3F vectors, ANOVA

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 956T300T

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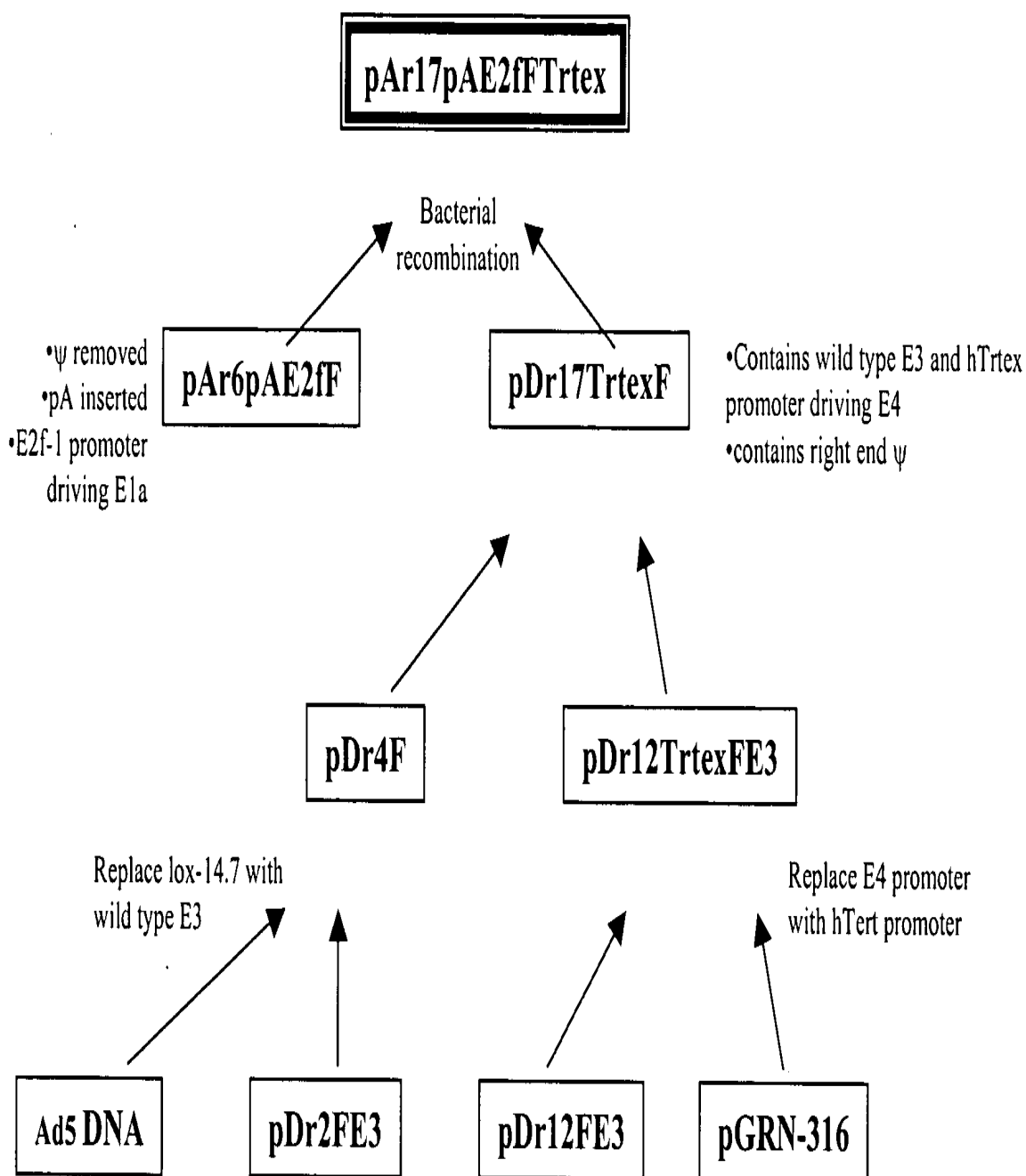
Figure 44. Spread of adenoviruses in Hep3B xenograft tumors detected by FACS.



p<0.05 between Ar6pAE2fhGmF and Ar6pAE2f(E3+,hGm,Dg19)F and Add/312, ANOVA
 p<0.05 between Ar6pAE2fhGmF and Ar6pAE2f(E3+,hGm,Dg19)F vectors, ANOVA

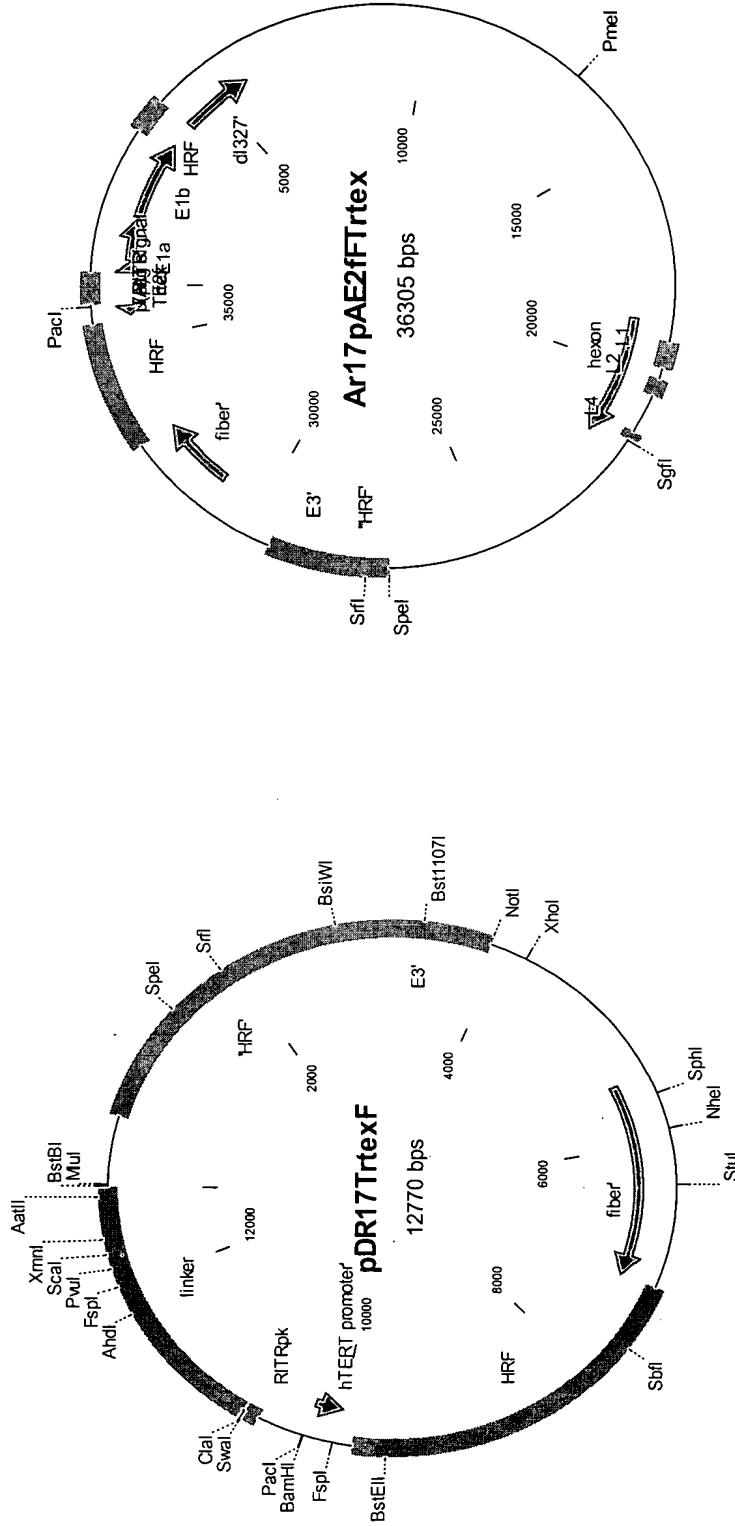
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Figure 45: Flowchart for construction of pAR17pAE2fFTrtex:



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Figure 46: Plasmids used to create oncolytic vector Ar17pAE2fTtrtex



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Figure 47: Sequence of the right end of Ar17pAE2fFTrtex (Seq ID NO:17).

35351 agtgctaaaa agcgaccgaa atagcccggg ggaatacata cccgcaggcg
35401 tagagacaac attacagccc ccataggagg tataacaaaa ttaataggag
35451 agaaaaacac ataaacacct gaaaaaccct cctgcctagg caaaatagca
35501 ccctcccgtt ccagaacaac atacagcgct tcacagcggc agcctaacag
35551 tcagccttac cagtaaaaaa gaaaacctat taaaaaaaca ccactcggat
35601 caattcgcgg ggggtggcgg ggccagggct tcccacgtgc gcagcaggac
35651 gcagcgctgc ctgaaactcg cgccgcgagg agagggcggg gccgcggaaa
35701 ggaaggggag gggctgggag ggcccggagg gggctgggcc ggggaccggg
35751 gaggggtcgg gacggggcgg ggtccgcgcg gaggaggcgg agctggaagg
35801 tgaaggggca ggacgggtgc ccgggtcccc agtccctccg ccacgtgggg
35851 ctaggatcct taattaagaa ttctacaatt cccaacacat acaagttact
35901 ccgccctaaa accctgggcg agtctccacg taaacgggtc aagtccccgc
35951 ggccctagac aaatattacg cgctatgagt aacacaaaat tattcagatt
36001 tcacttcctc ttattcagtt ttcccgcgaa aatggccaaa tcttactcgg
36051 ttacgcccac atttactaca acatccgcct aaaaccgcgc gaaaattgtc
36101 acttcctgtg tacaccggcg cacaccaaaa acgtcacttt tgccacatcc
36151 gtcgcttaca tgtgttccgc cacacttgca acatcacact tccgccacac
36201 tactacgtca cccgccccgt tcccacgccc cgcgccacgt cacaaactcc
36251 accccctcat tatcatattg gcttcaatcc aaaataagggt atattattga
36301 tgatg

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Figure 48: Diagram of Ar17pAE2fTrtex.

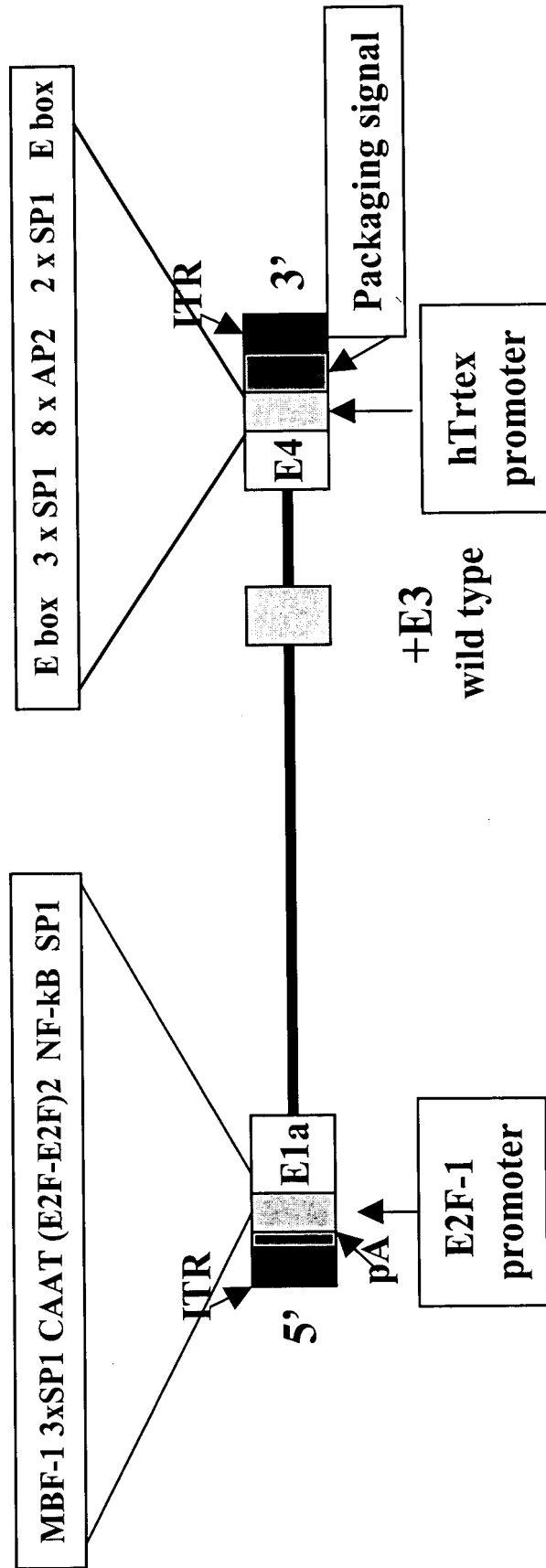


Figure 49. E4 expression is dependent on the hTERT promoter

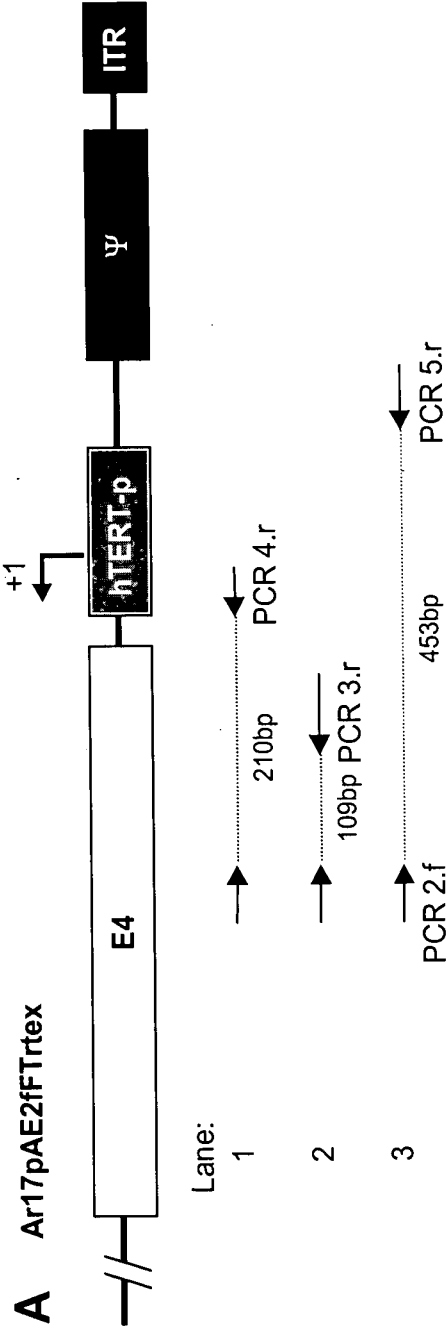


Figure 50. E4 transcription start sites in Ar17pAE2fTrex (Seq ID NO:21)

35521 ATACAGCGCT TCACAGCGGC AGCCTAACAG TCAGCCTTAC CAGTAAAAAA GAAACCTAT
ExtP1
35581 TAAAAAACA CCACTCGGAT CAATTGCGG GGTG[←]CCCG GGCAGGGCT TCCACGTGC
35641 GCAGCAGGAC GCAGCGCTGC CTGAAATCG CGCCGCGAGG AGAGGGCGGG GCCGCGGAAA
35701 AGGAACGGGA CGGGCTGGA TGGCCCGGA GGGCTGGC CGGGACCCG GGAAGG[←]TTC
35761 GGGACGGGC GGGTTCCG GCGACGAGG CGGAGCTGA AGTGAAGG GCAGGACCG
35821 TGCCCCGGTC CCCAGTCCCT CCGCCACGTG GGGTAGGAT CCTTAATTAA GAATTCTACA
35881 ATTCCCAACA CATAAAGTT ACTCCGCCCT AAAACCCCTG GCG

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Figure 51. Efficacy of Ar17pAE2fFTrex in Hep3B model.

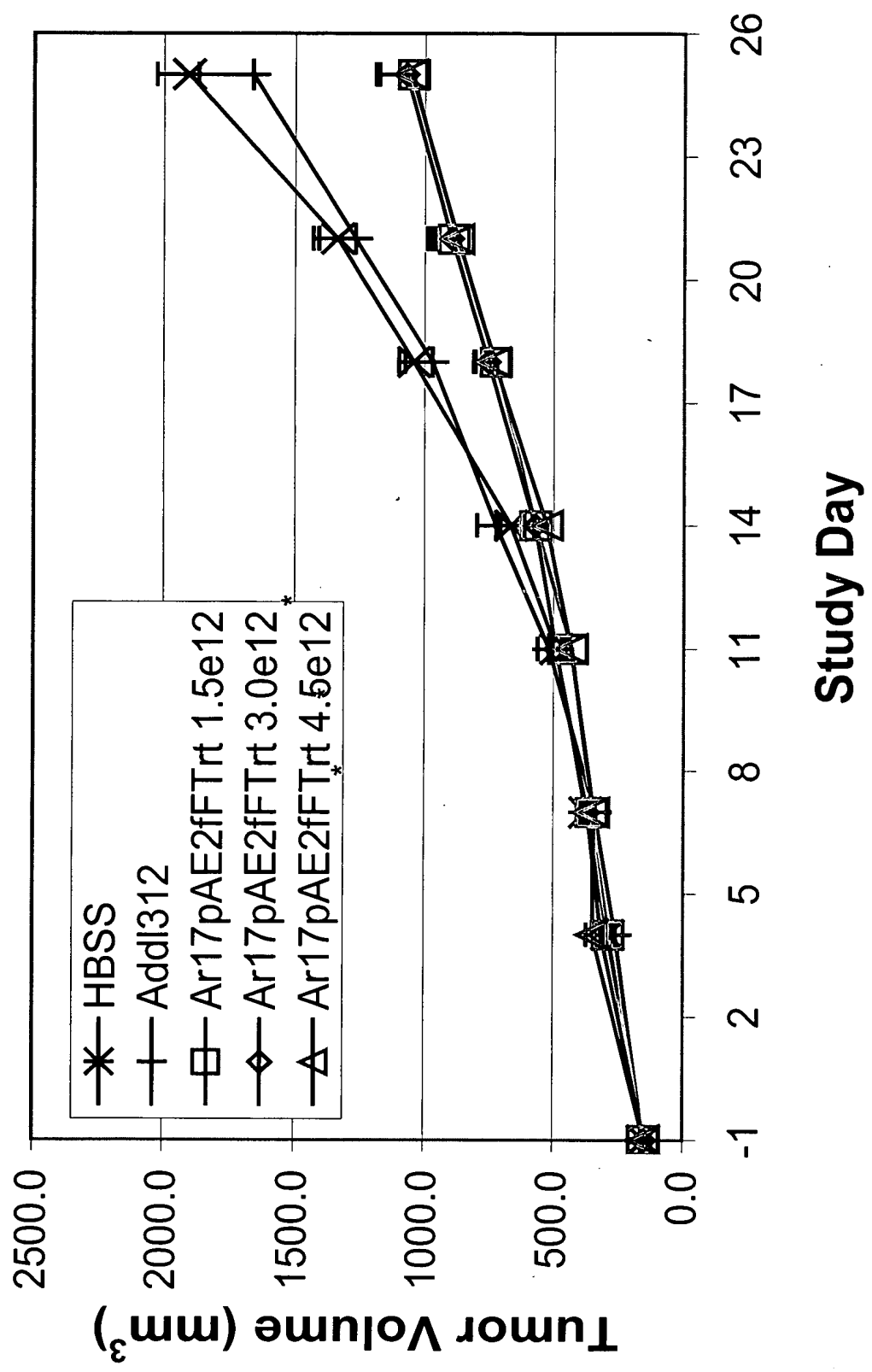
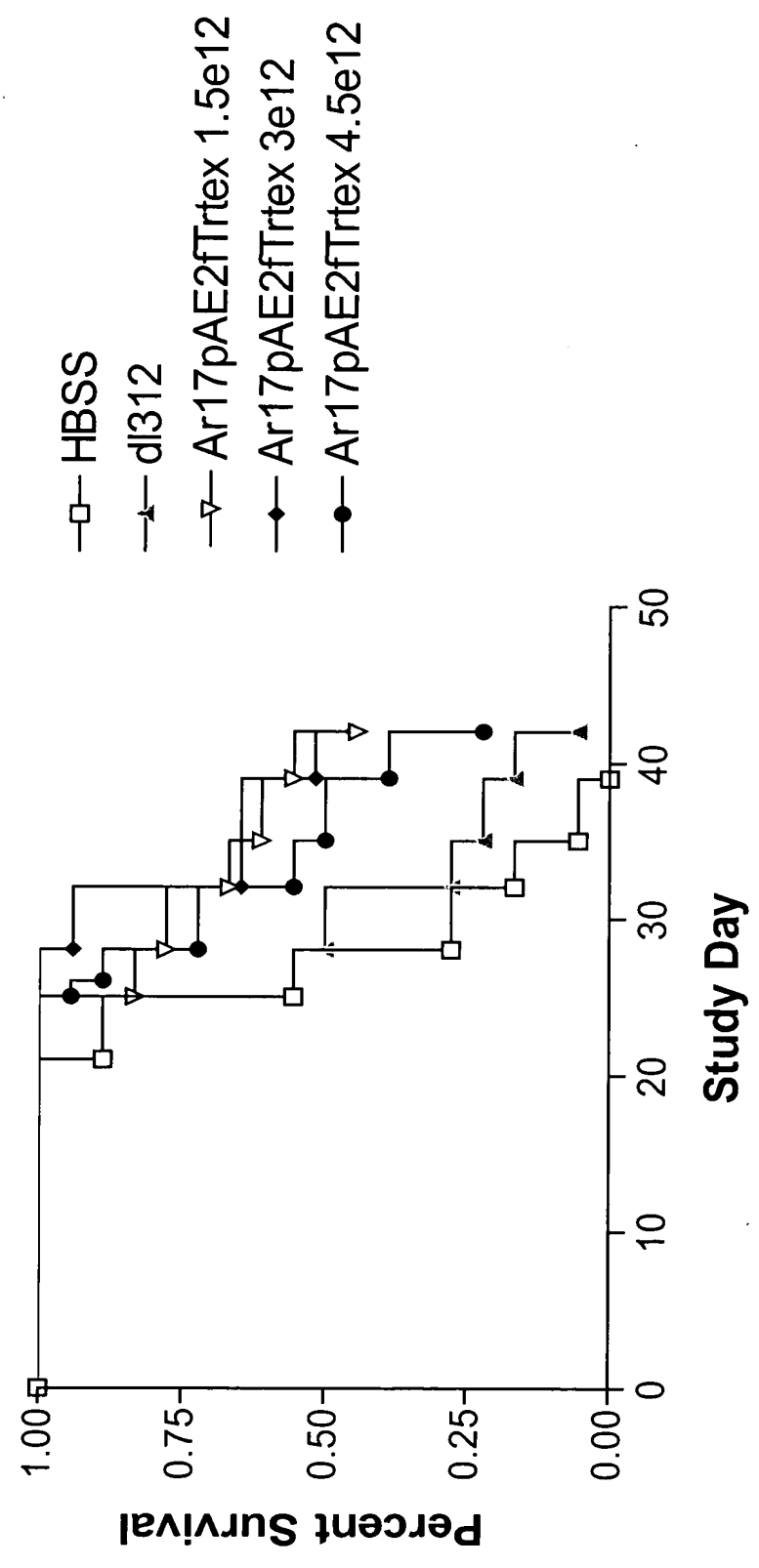
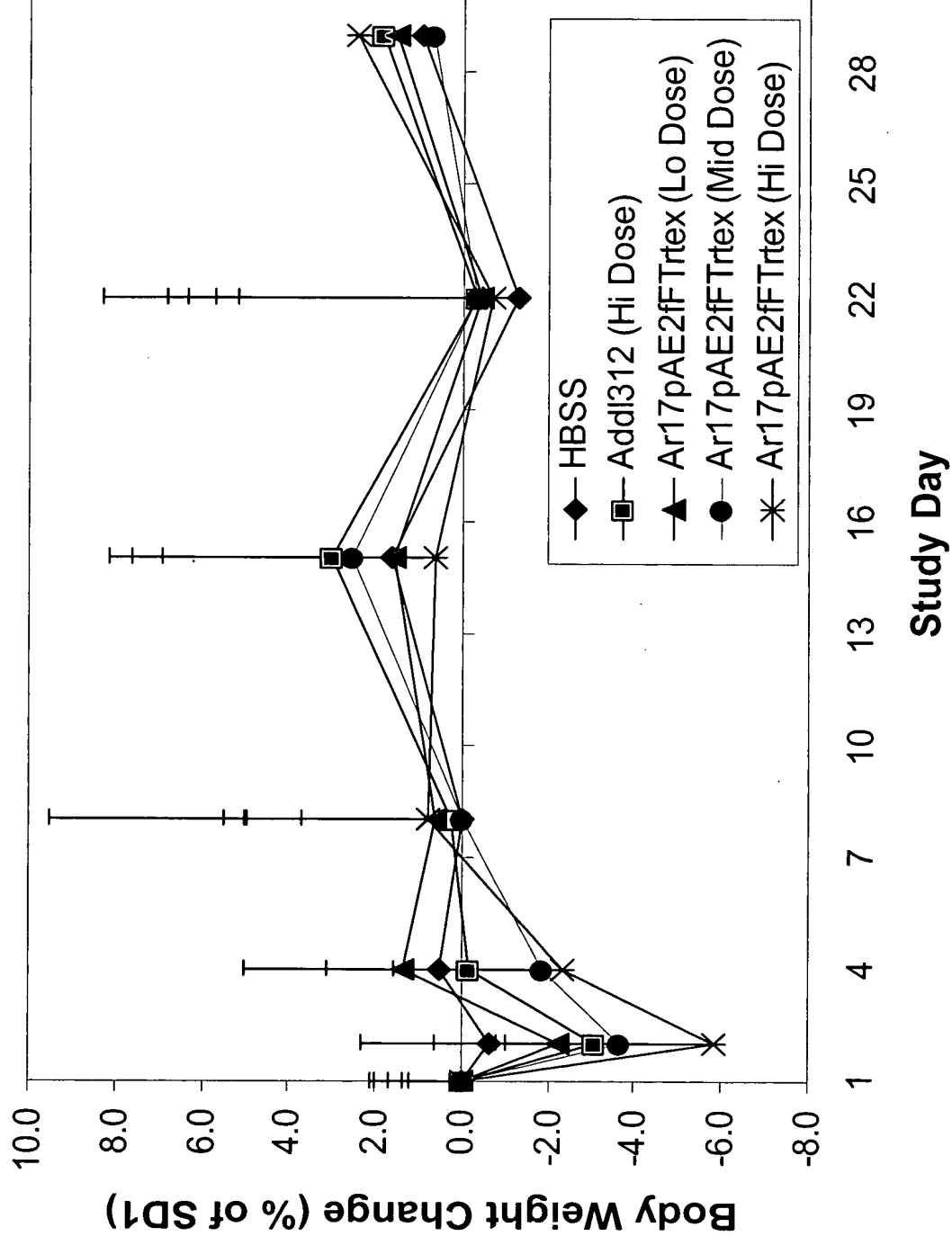


Figure 52. Effect of Ar17pAE2fTtrtex on survival.



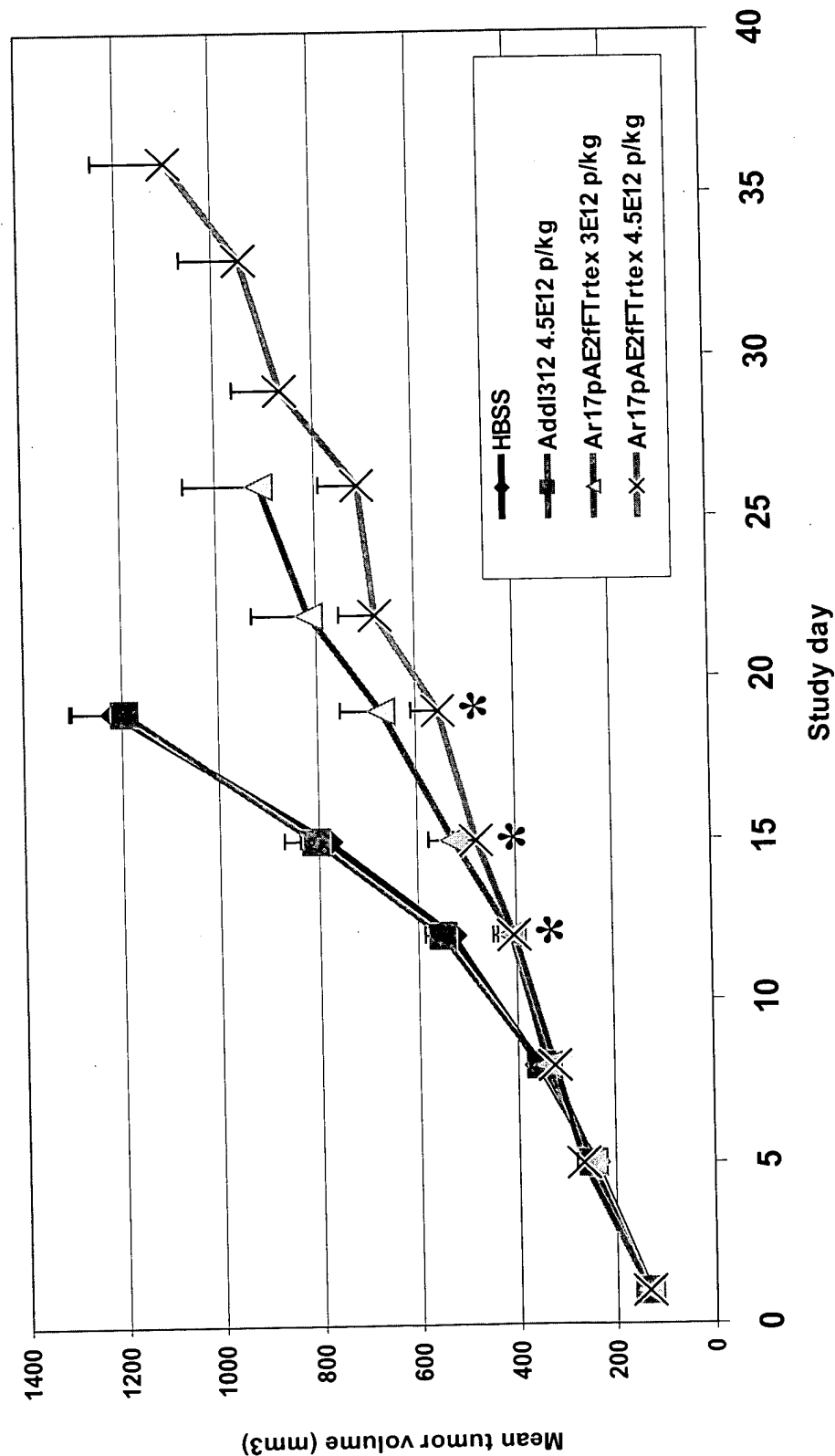
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Figure 53. Body weight changes



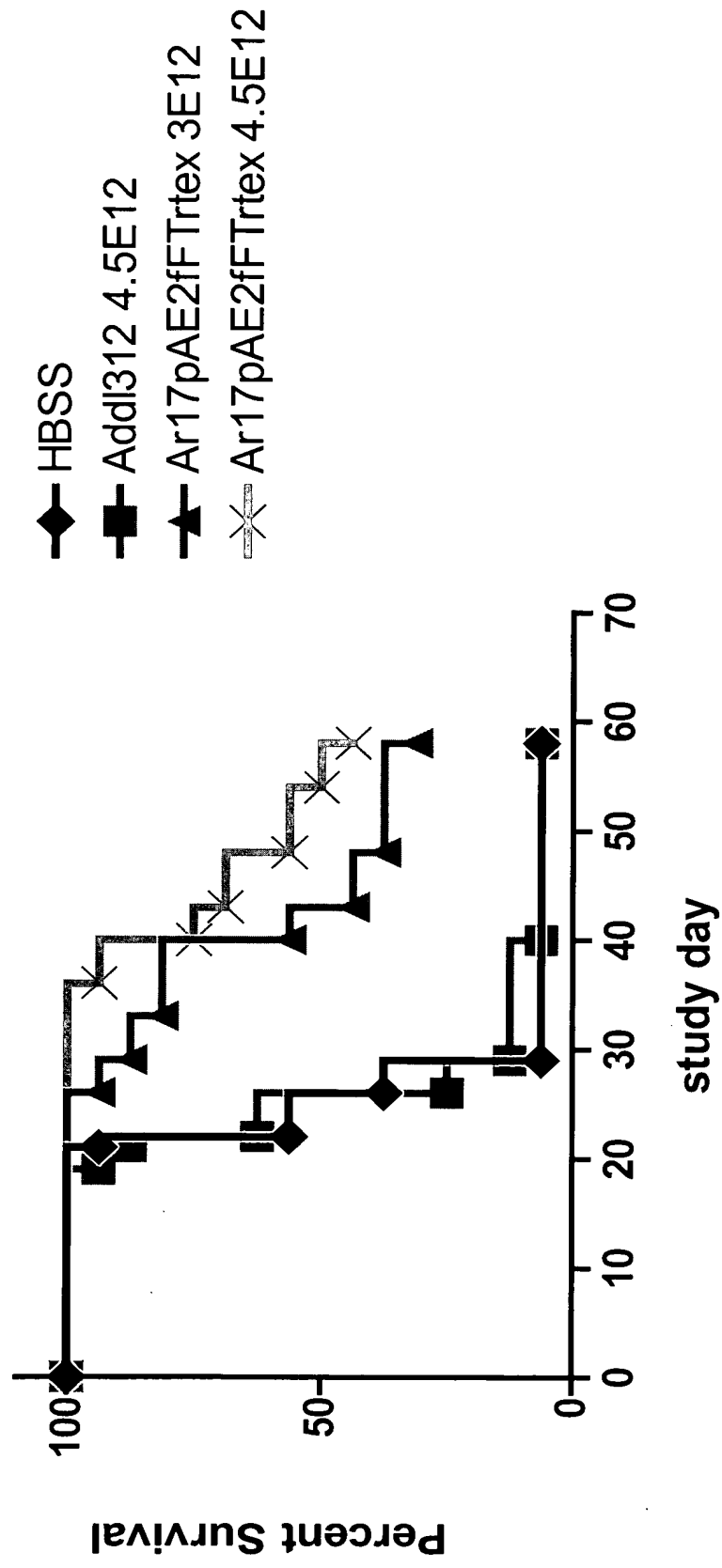
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Figure 54. Efficacy of Ar17pAE2fTrtex in Hep3B model.



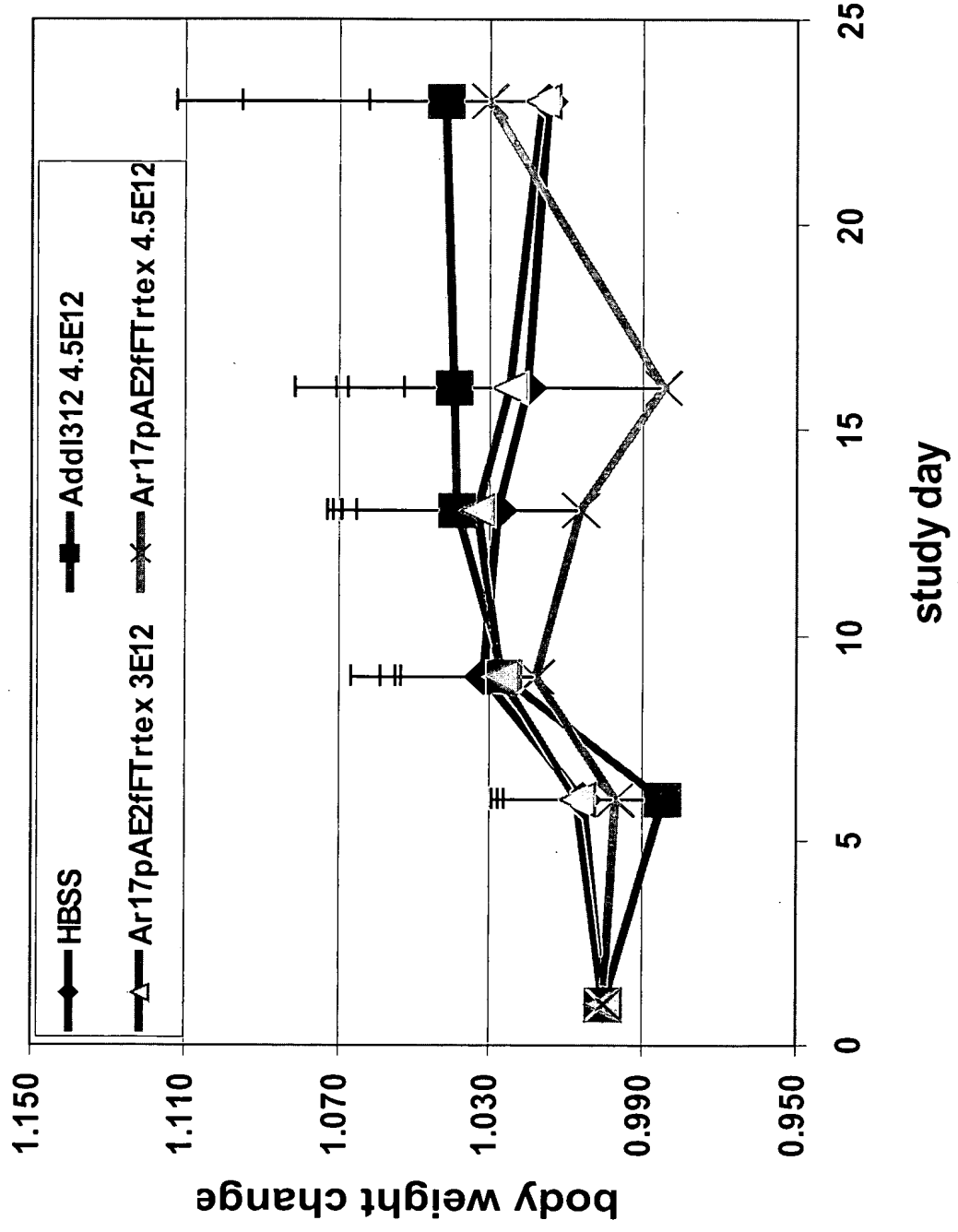
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Figure 55. Effect of Ar17pAE2fTrtex on survival.



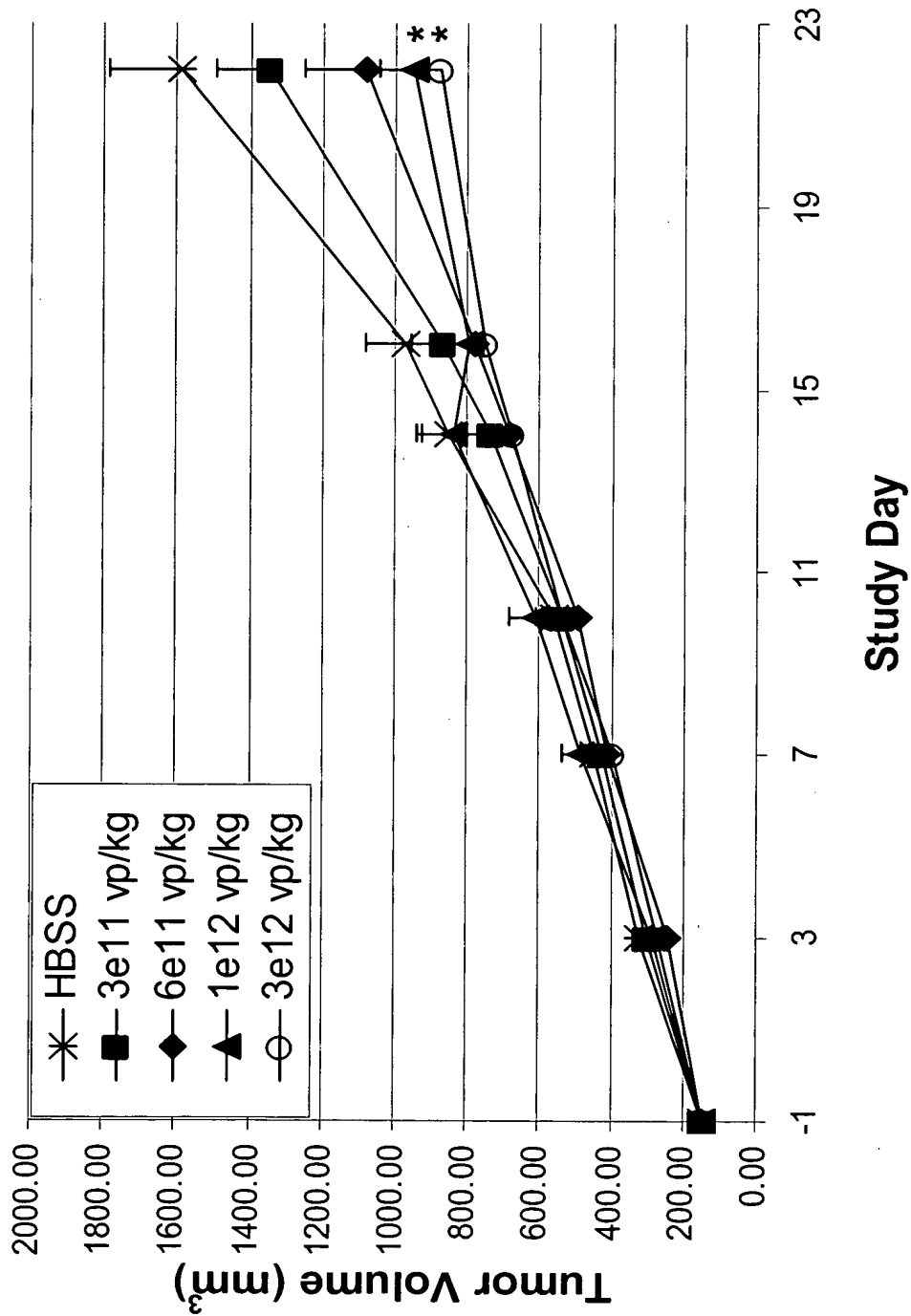
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Figure 56. Body weight changes



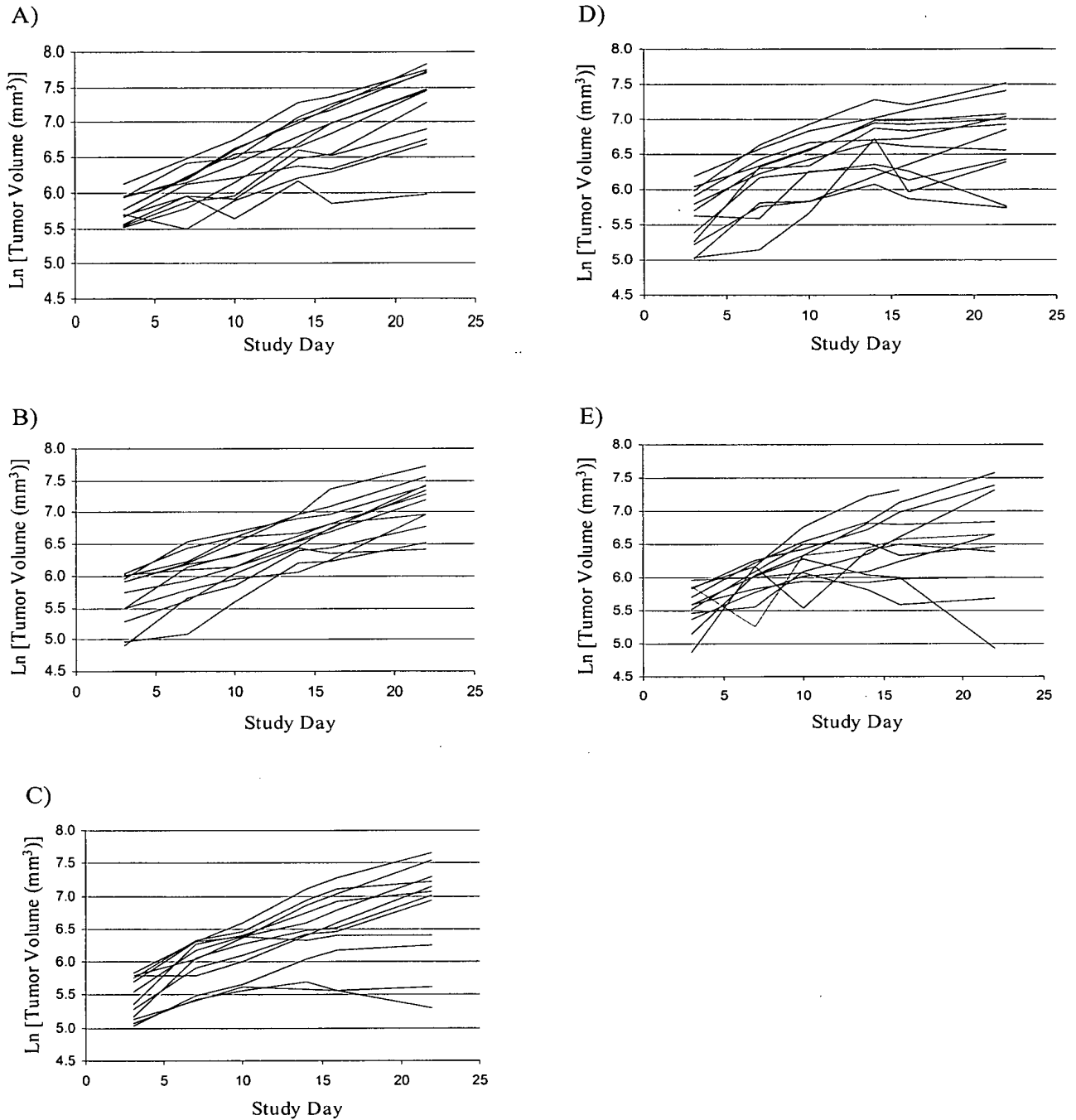
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Figure 57 Dose-dependent anti-tumor efficacy



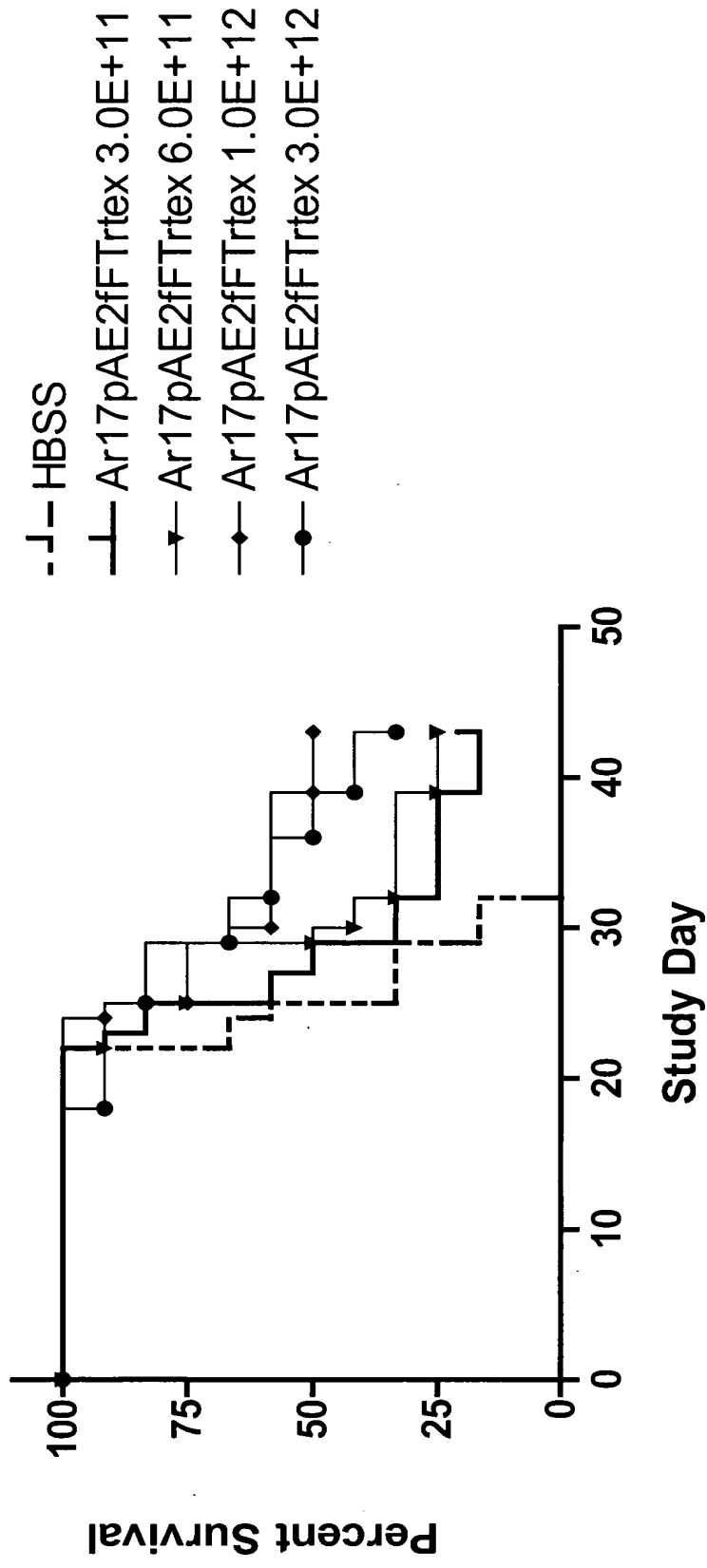
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Figure 58. Individual tumor volumes following intravenous administration of Ar17pAE2fFTrtex



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Figure 59. Effect of Ar17pAE2fFTrtex on survival.



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Figure 60. Body weight (% change)

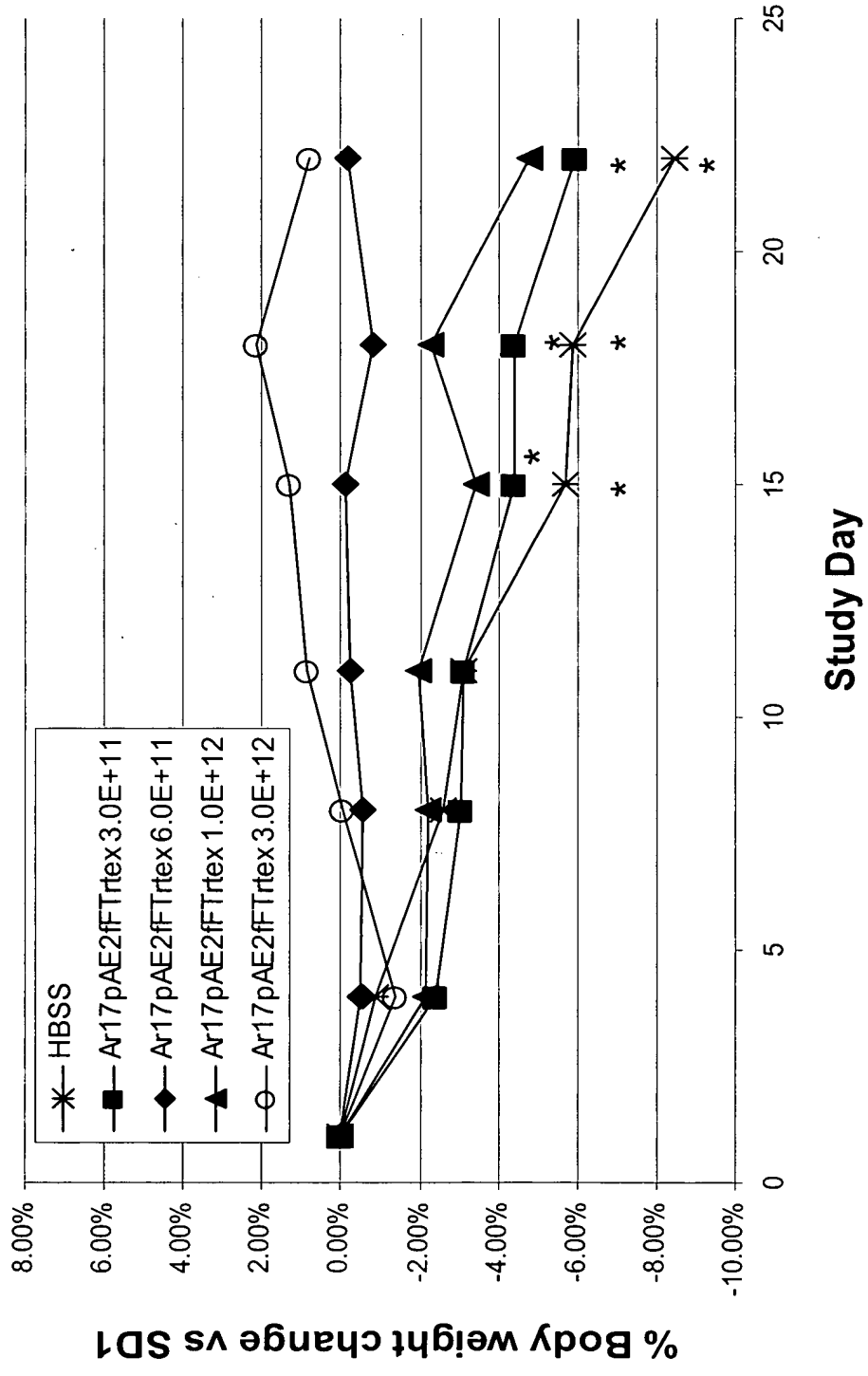
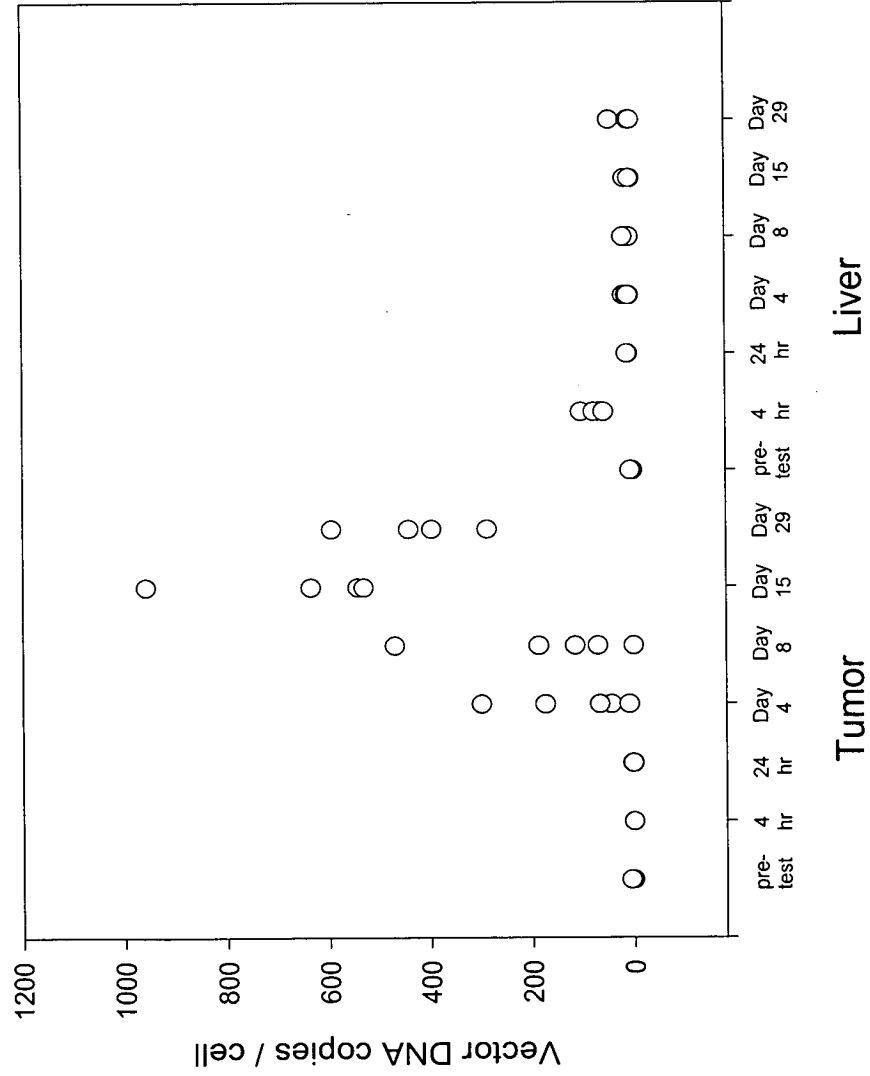


Figure 61.



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Figure 62. Effect on body weight in SCID mice

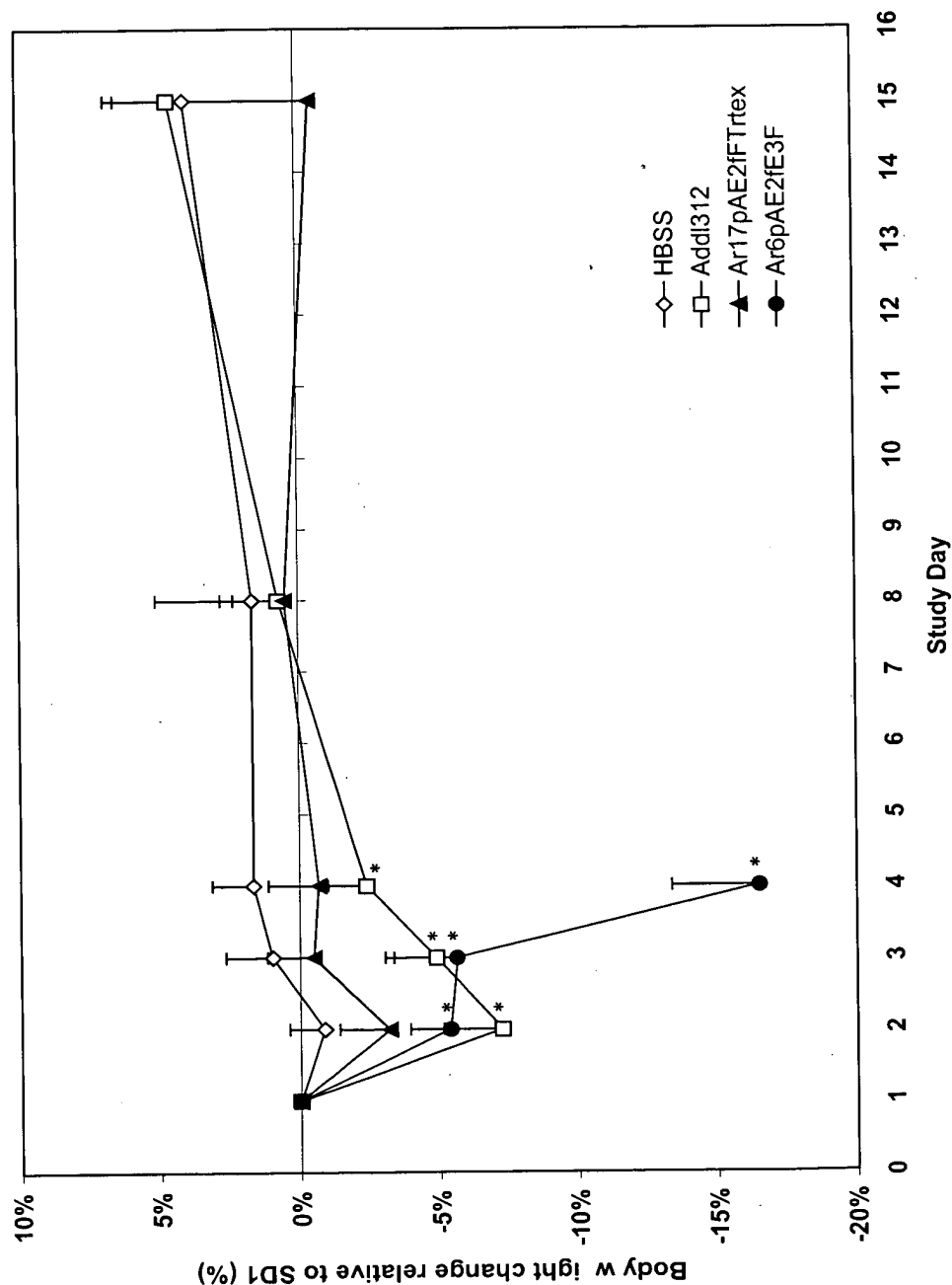
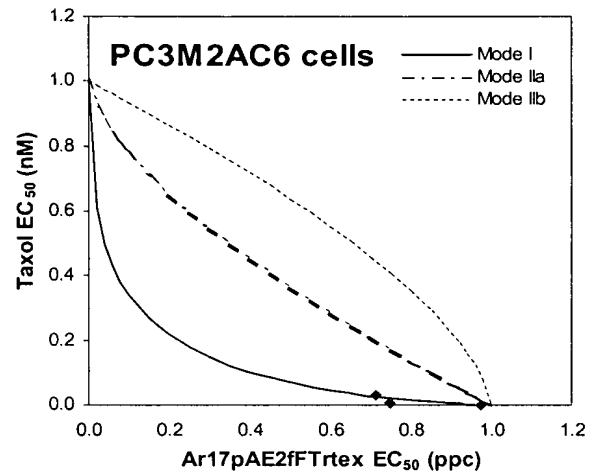
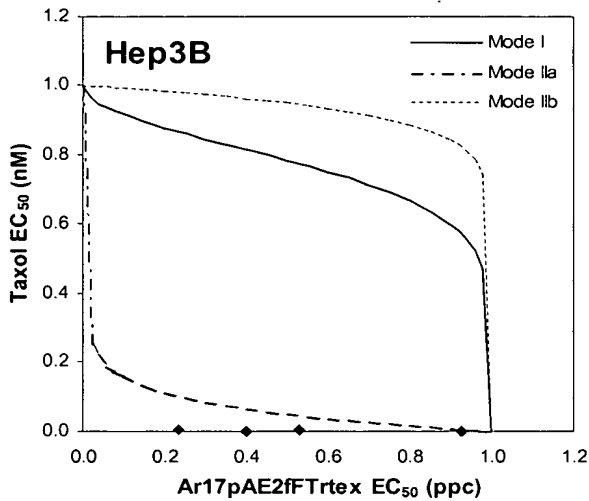


Figure 63. Improved isobologram with additivity envelope for Ar17pAE2fFTrtex and Taxol against Hep 3B and PC3M.2AC6 cells.

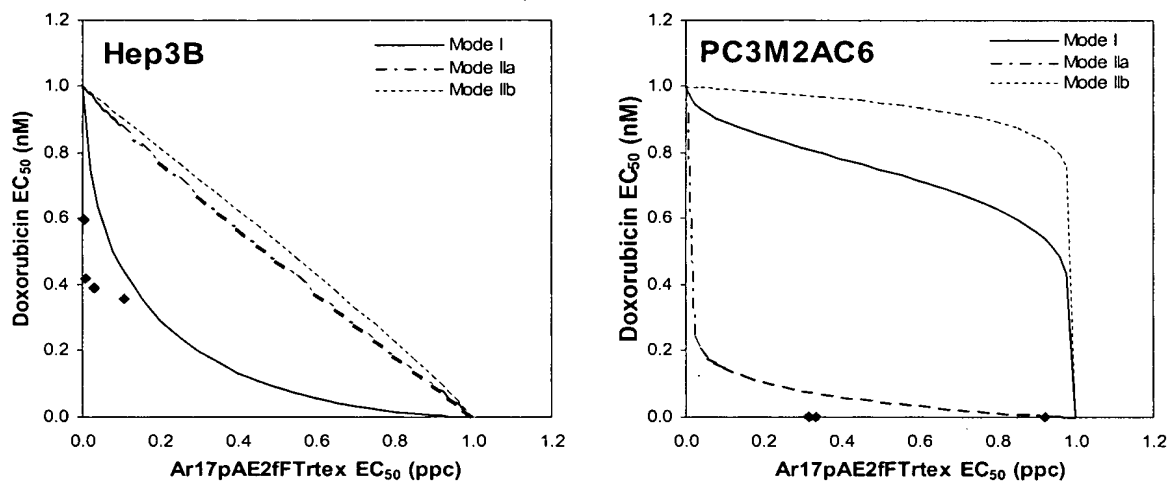


MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
8.3e-05	0.23	0.0043	synergy
3.3e-04	0.53	0.0024	synergy
1.3e-03	0.40	0.00046	synergy
5.3e-03	0.93	0.00027	synergy

MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
0.02	3.4	1.3	antagonism
0.2	0.71	0.028	synergy
2	0.75	0.003	synergy
20	0.97	0.0004	synergy

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Figure 64. Improved isobologram with additivity envelope for Ar17pAE2fFTrtex and Doxorubicin against Hep 3B and PC3M.2AC6 cells.

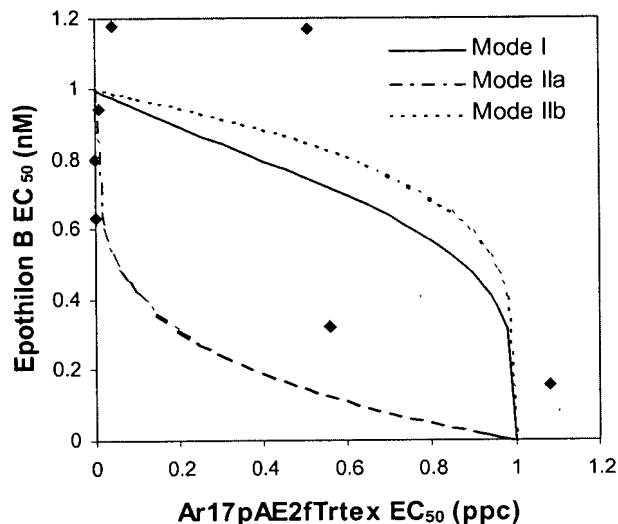


MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
1.3e-05	0.0028	0.60	synergy
5.0e-05	0.0078	0.42	synergy
2.0e-04	0.029	0.39	synergy
8.0e-04	0.11	0.36	synergy

MR (ppc/nM)	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
1	2.2	0.015	antagonism
10	0.92	6.1e-4	synergy
100	0.34	2.2e-5	synergy
1000	0.32	2.1e-6	synergy

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Figure 65. Improved isobologram with additivity envelope for Ar17pAE2fTrtex and Epothilone B against Hep 3B cells.

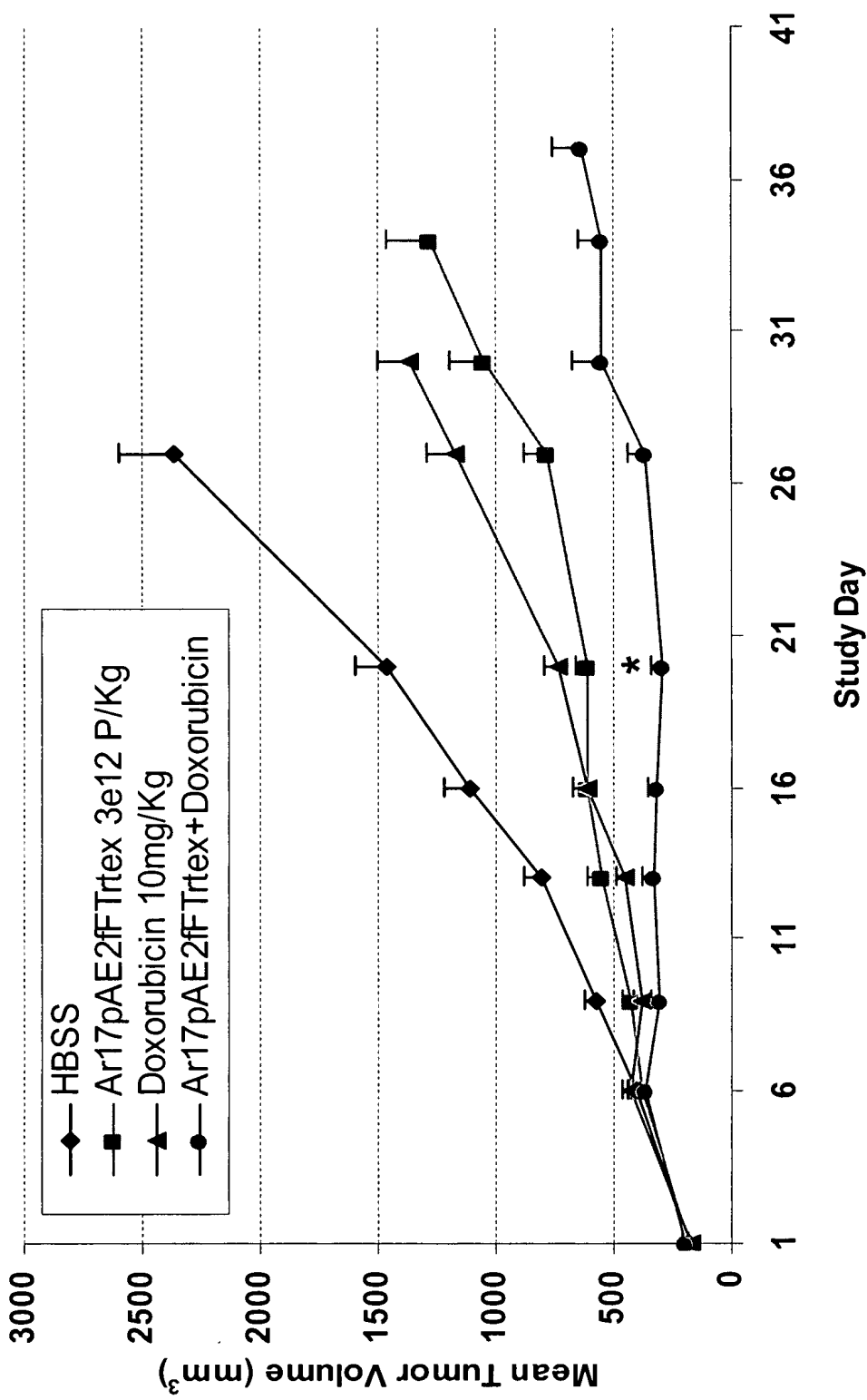


	Virus EC ₅₀ ^b	Chemo EC ₅₀ ^b	Effect
Virus alone	1	0	-
Chemo alone	0	1	-
3.1e-06	0.00045	0.63	synergy
1.3e-05	0.0018	0.80	synergy
5.0e-05	0.0084	0.95	synergy
2.0e-04	0.042	1.2	antagonism
8.0e-04	0.18	1.6	antagonism
3.2e-03	0.51	1.2	antagonism
1.3e-02	0.56	0.32	additivity
5.1e-02	1.1	0.06	antagonism

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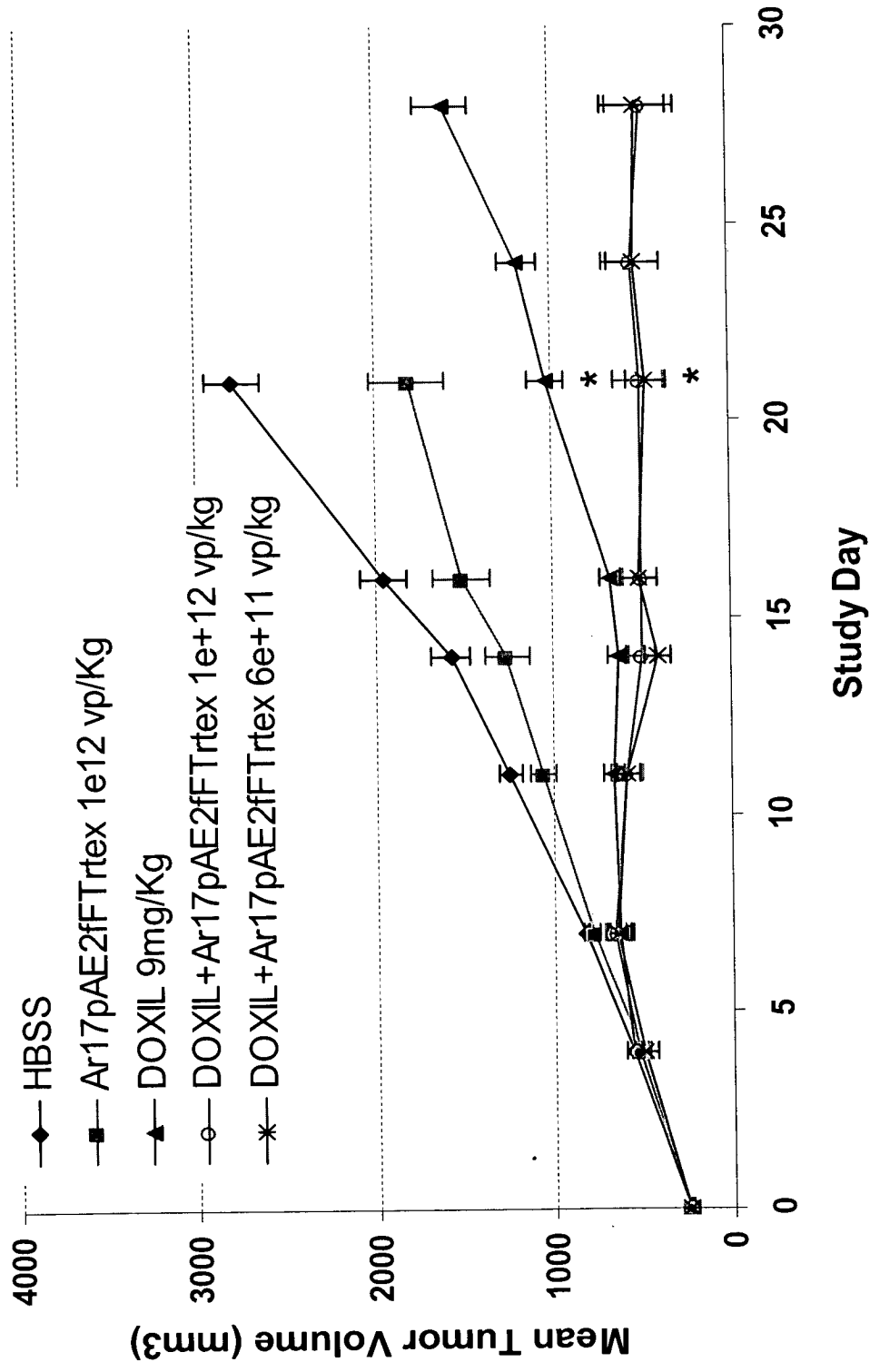
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Figure 66. Doxorubicin Combination: Mean Tumor Volumes



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Figure 67. Doxil® Combination Mean Tumor Volumes



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Figure 68. Cytotoxicity assessed in primary human hepatocytes

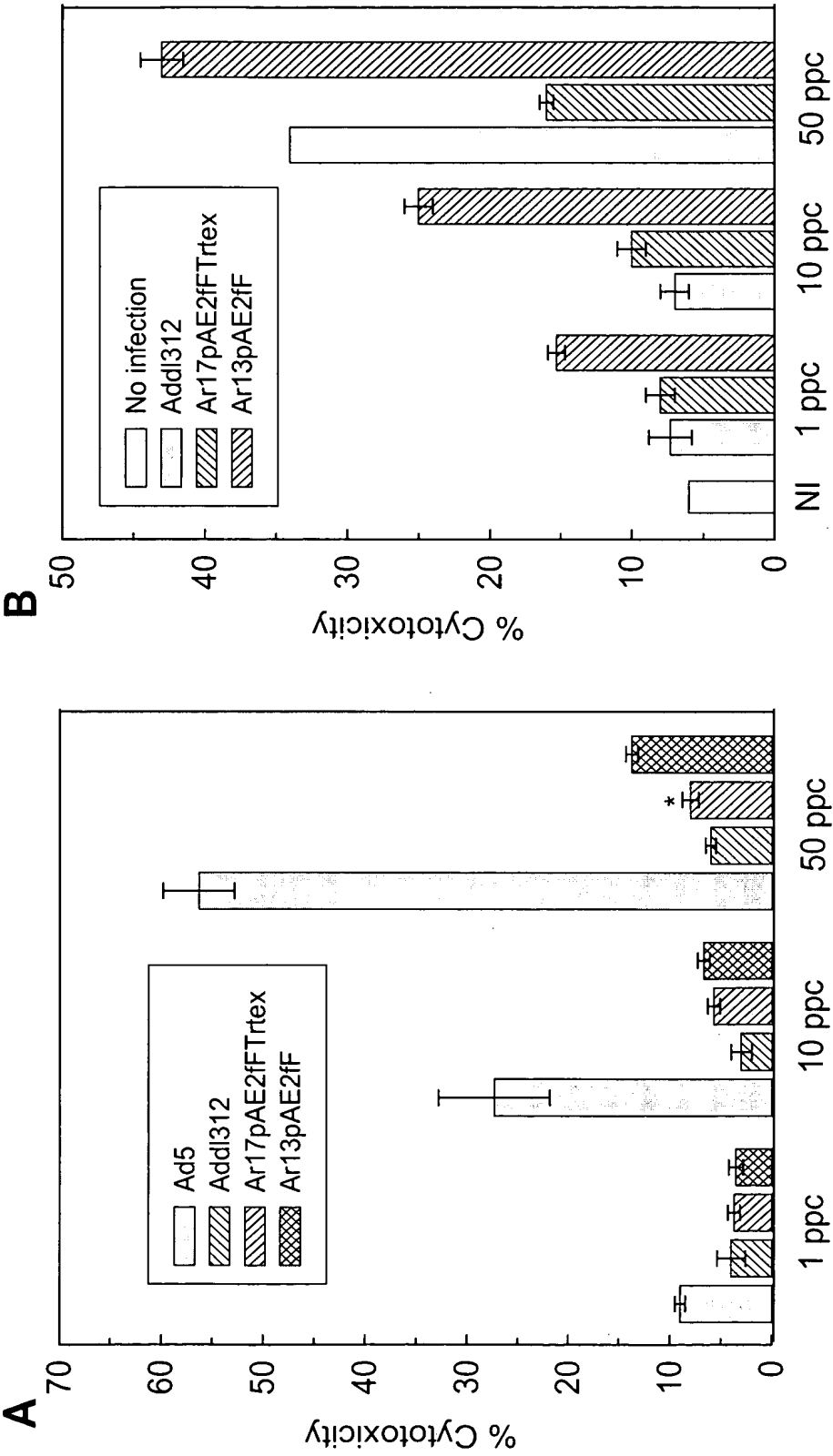
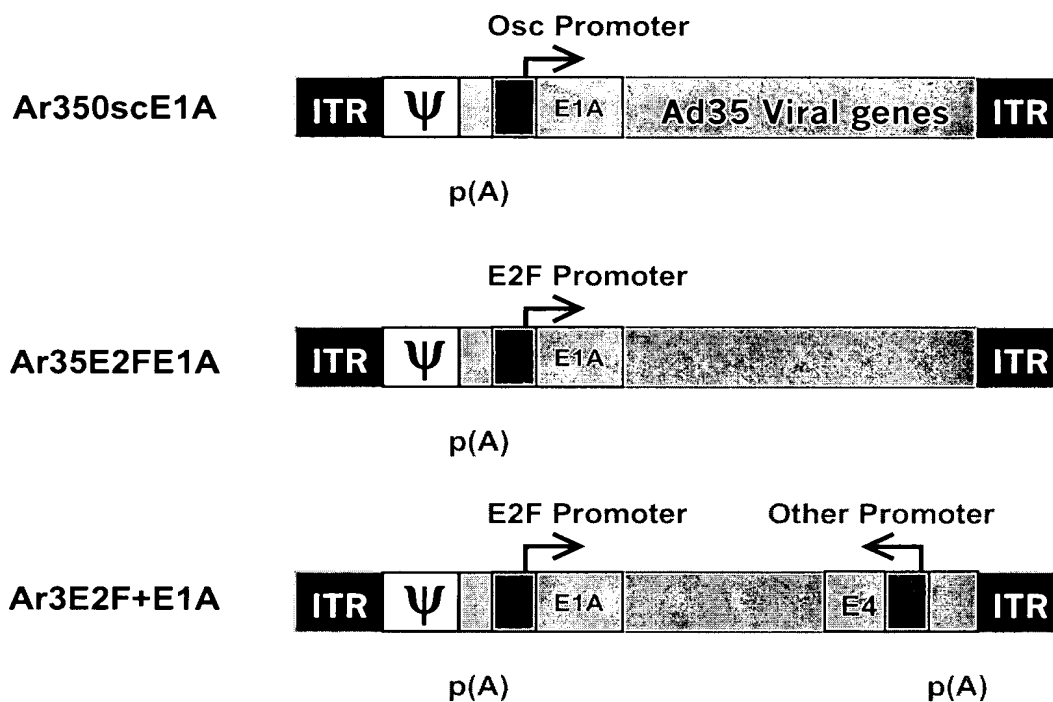


Figure 69

Ad35-Based Oncolytic Vectors



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Figure 70

